(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 October 2003 (23.10.2003)

PCT

(10) International Publication Number
WO 03/086344 A1

(51) International Patent Classification[7]: A61K 9/00, 9/48, 9/52, 9/54, 9/20, 9/22, 9/24, 9/14

(21) International Application Number: PCT/US02/40809

(22) International Filing Date:
20 December 2002 (20.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

10/027,366	20 December 2001 (20.12.2001)	US
10/027,837	20 December 2001 (20.12.2001)	US
10/027,609	20 December 2001 (20.12.2001)	US
10/028,590	20 December 2001 (20.12.2001)	US
10/027,866	20 December 2001 (20.12.2001)	US
10/028,595	20 December 2001 (20.12.2001)	US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ANTIBIOTIC PRODUCT, USE AND FORMULATION THEREOF

(57) Abstract: An antibiotic product is comprised of at least three dosages forms, each of which has a different release profile, with the C_{max} for the antibiotic product being reached in less than about twelve hours. In one embodiment, there is an immediate release dosage form, as well as two or more delayed release dosage forms, with each of the dosage forms having a different release profile, wherein each reaches a C_{max} at different times.

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ANTIBIOTIC PRODUCT, USE AND FORMULATION THEREOF

This application claims the benefits of U.S. Application Serial No. 10/027,366, filed December 20, 2001; U.S. Application Serial No. 10/027,866, filed December 20, 2001; U.S. Application Serial No. 10/028,590, filed December 20, 2001; U.S. Application Serial No. 10/028,595, filed December 20, 2001; U.S. Application Serial No. 10/027,837, filed December 20, 2001; and U.S. Application Serial No. 10/027,609, filed December 20, 2001. Each of the foregoing is a continuation-in-part of U.S. Application Serial No. 09/792,092, filed on February 22, 2000, which is a continuation-in-part of U.S. Application Serial No. 09/687,229, filed on October 13, 2000, and also claims the priority of U.S. Provisional Application Serial No. 60/184,546 filed on February 24, 2000.

This invention relates to an antibiotic product, as well as the use and formulation thereof.

The invention further relates to a levofloxacin antibiotic product, including derivatives thereof such as salts, esters, metabolites, etc.

The invention further relates to a metronidazole antibiotic product and derivatives thereof, such as salts, esters, metabolites, etc.

The invention further relates to a tetracycline antibiotic product and in particular doxycycline and its derivatives, salts, hydrates, esters, metabolites, etc.

The invention further relates to an erythromyacin antibiotic product, in particular an erythromyacin derivative or a macrolide or a ketolite (including derivatives thereof such as salts, esters, etc.); in particular Clarithromycin.

The invention further relates to (a) fluroquinilone antibiotic products and in particular ciprofloxacin and its derivatives such as salts, esters, bases, etc., metabolites, etc.

The invention further relates to betalactam antibiotic products and in particular to products that include a cephalosporin, such as cefuroxime and/or cefpodoxime or a penicillin such as amoxicillin or dicloxacillin, as well as derivatives, metabolites and any active isomers thereof.

A wide variety of antibiotics have been used, and will be used, in order to combat bacterial infection. In general, such antibiotics can be administered by a repeated dosing of immediate release dosage forms, which results in poor compliance or as a controlled release formulation (slow release) at higher administered doses. The present invention is directed to providing for an improved antibiotic product.

In accordance with one aspect of the present invention, there is provided an antibiotic pharmaceutical product which is comprised of at least two, preferably at least three, antibiotic dosage forms. Such dosage forms are formulated so that each of the dosage forms has a different release profile.

In a particularly preferred embodiment, there are at least two, preferably at least three dosage forms, each of which has a different release profile and the release profile of each of the dosage forms is such that the dosage forms each start release of the antibiotic contained therein at different times after administration of the antibiotic product.

Thus, in accordance with an aspect of the present invention, there is provided a single or unitary antibiotic product that has contained therein at least two, preferably at least three antibiotic dosage forms, each of which has a different release profile, whereby the antibiotic contained in each of such dosage forms is released at different times.

In accordance with a further aspect of the invention, the antibiotic product may be comprised of at least four different dosage forms, each of which starts to release the antibiotic contained therein at different times after administration of the antibiotic product.

The antibiotic product generally does not include more than five dosage forms with different release times.

In accordance with a preferred embodiment, the antibiotic product has an overall release profile such that when administered the maximum serum concentration of the total antibiotic released from the product is reached in less than twelve hours, preferably in less than eleven hours. In an embodiment, the maximum serum concentration of the total antibiotic released from the antibiotic product is achieved no earlier than four hours after administration.

In accordance with one preferred embodiment of the invention, there are at least three dosage forms. One of the at least three dosage forms is an immediate release dosage form whereby initiation of release of the antibiotic therefrom is not substantially delayed after administration of the antibiotic product. The second and third of the at least three dosage forms is a delayed dosage form (which may be a pH sensitive or a non-pH sensitive delayed dosage form, depending on the type of antibiotic product), whereby the antibiotic released therefrom is delayed until after initiation of release of the antibiotic from the immediate release dosage form. More particularly, the antibiotic release from the second of the at least two dosage forms achieves a C_{max} (maximum serum concentration in the serum) at a time after the antibiotic released from the first of the at least three dosage forms achieves a C_{max} in the serum, and the antibiotic released from the third dosage form achieves a C_{max} in the serum after the C_{max} of antibiotic released from the second dosage form.

In one embodiment, the second of the at least two dosage forms initiates release of the antibiotic contained therein at least one hour after the first dosage form, with the initiation of the release therefrom generally occurring no more than six hours after initiation of release of antibiotic from the first dosage form of the at least three dosage forms.

In general, the immediate release dosage form produces a C_{max} for the antibiotic released therefrom within from about 0.5 to about 2 hours, with the second dosage form of the at least three dosage forms producing a C_{max} for the antibiotic released therefrom in no more than about four hours. In general, the C_{max} for such second dosage form is achieved no earlier than two hours after administration of the antibiotic product; however, it is possible within the scope of the invention to achieve C_{max} in a shorter period of time.

As hereinabove indicated, the antibiotic product may contain at least three or at least four or more different dosage forms. For example, if the antibiotic product includes a third dosage form, the antibiotic released therefrom reaches a C_{max} at a time later than the C_{max} is achieved for the antibiotic released from each of the first and second dosage forms. In a preferred embodiment, release of antibiotic from the third dosage form is started after initiation of release of antibiotic from both the first dosage form and the second dosage form. In one embodiment, C_{max} for antibiotic release from the third dosage form is achieved within eight hours.

In another embodiment, the antibiotic product contains at least four dosage forms, with each of the at least four dosage forms having different release profiles, whereby the antibiotic release from each of the at least four different dosage forms achieves a C_{max} at a different time.

As hereinabove indicated, in a preferred embodiment, irrespective of whether the antibiotic contains at least two or at least three or at least four different dosage forms each with a different release profile, C_{max} for all the antibiotic released from the antibiotic product is achieved in less than twelve hours, and more generally is achieved in less than eleven hours.

In a preferred embodiment, the antibiotic product is a once a day product, whereby after administration of the antibiotic product, no further product is administered during the day; i.e., the preferred regimen is that the product is administered only once over a twenty-four hour period. Thus, in accordance with the present invention, there is a single administration of an antibiotic product with the antibiotic being released in a manner such that overall antibiotic release is effected with different release profiles in a manner such that the overall C_{max} for the antibiotic product is reached in less than twelve hours. The term single administration means that the total antibiotic administered over a twenty-four hour period is administered at the same time, which can be a single tablet or capsule or two or more thereof, provided that they are administered at essentially the same time.

Applicant has found that a single dosage antibiotic product comprised of at least three antibiotic dosage forms each having a different release profile is an improvement over a single dosage antibiotic product comprised of an antibiotic dosage form having a single release profile. Each of the dosage forms of antibiotic in a pharmaceutically acceptable carrier may have one or more antibiotics and each of the dosage forms may have the same antibiotic or different antibiotics.

It is to be understood that when it is disclosed herein that a dosage form initiates release after another dosage form, such terminology means that the dosage form is designed and is intended to produce such later initiated release. It is known in the art, however, notwithstanding such design and intent, some "leakage" of antibiotic may occur. Such "leakage" is not "release" as used herein.

If at least four dosage forms are used, the fourth of the at least four dosage form may be a sustained release dosage form or a delayed release dosage form. If the fourth dosage form is a sustained release dosage form, even though C_{max} of the fourth dosage form of the at least four dosage forms is reached after the C_{max} of each of the other dosage forms is reached, antibiotic release from such fourth dosage form may be initiated prior to or after release from the second or third dosage form.

The antibiotic product of the present invention, as hereinabove described, may be formulated for administration by a variety of routes of administration. For example, the antibiotic product may be formulated in a way that is suitable for topical administration; administration in the eye or the ear; rectal or vaginal administration; as nose drops; by inhalation; as an injectable; or for oral administration. In a preferred embodiment, the antibiotic product is formulated in a manner such that it is suitable for oral administration.

For example, in formulating the antibiotic product for topical administration, such as by application to the skin, the at least two different dosage forms, each of which contains an antibiotic, may be formulated for topical administration by including such dosage forms in an oil-in-water emulsion, or a water-in-oil emulsion. In such a formulation, the immediate release dosage form is in the continuous phase, and the delayed release dosage form is in a discontinuous phase. The formulation may also be produced in a manner for delivery of three dosage forms as hereinabove described. For example, there may be provided an oil-in-water-in-oil emulsion, with oil being a continuous phase that contains the immediate release component, water dispersed in the oil containing a first delayed release dosage form, and oil dispersed in the water containing a third delayed release dosage form.

It is also within the scope of the invention to provide an antibiotic product in the form of a patch, which includes antibiotic dosage forms having different release profiles, as hereinabove described.

In addition, the antibiotic product may be formulated for use in the eye or ear or nose, for example, as a liquid emulsion. For example, the dosage form may be coated with a hydrophobic polymer whereby a dosage form is in the oil phase of the emulsion, and a dosage form may be coated with hydrophilic polymer, whereby a dosage form is in the water phase of the emulsion.

Furthermore, the antibiotic product with at least three different dosage forms with different release profiles may be formulated for rectal or vaginal administration, as known in the art. This may take the form of a cream or emulsion, or other dissolvable dosage form similar to those used for topical administration.

As a further embodiment, the antibiotic product may be formulated for use in inhalation therapy by coating the particles and micronizing the particles for inhalation.

In a preferred embodiment, the antibiotic product is formulated in a manner suitable for oral administration. Thus, for example, for oral administration, each of the dosage forms may be used as a pellet or a particle, with a pellet or particle then being formed into a unitary pharmaceutical product, for example, in a capsule, or embedded in a tablet, or suspended in a liquid for oral administration.

Alternatively, in formulating an oral delivery system, each of the dosage forms of the product may be formulated as a tablet, with each of the tablets being put into a capsule to produce a unitary antibiotic product. Thus, for example, antibiotic products may include a first dosage form in the form of a tablet that is an immediate release tablet, and may also include two or more additional tablets, each of which provides for a delayed release of the antibiotic, as hereinabove described, whereby the C_{max} of the antibiotic released from each of the tablets is reached at different times, with the C_{max} of the total antibiotic released from the antibiotic product being achieved in less than twelve hours.

The formulation of an antibiotic product including at least three dosage forms with different release profiles for different routes of administration is deemed to be within the skill of the art from the teachings herein. As known in the art, with respect to delayed release, the time of release can be controlled by the concentration of antibiotics in the coating and/or the thickness of the coating.

In formulating an antibiotic product in accordance with the invention, in one embodiment, the immediate release dosage form of the product generally provides from about 20% to about 50% of the total dosage of antibiotic to be delivered by the product, with such immediate release dosage forms generally providing at least 25% of the total dosage of the antibiotic to be delivered by the product. In many cases, the immediate release dosage form provides from about 20% to about 30% of the total dosage of antibiotic to be delivered by the product; however, in some cases it may be

desirable to have the immediate release dosage form provide for about 45% to about 50% of the total dosage of antibiotic to be delivered by the product.

The remaining dosage forms deliver the remainder of the antibiotic. If more than one delayed release dosage form is used, in one embodiment, each of the delayed release dosage forms may provide about equal amounts of antibiotic; however, they may also be formulated so as to provide different amounts.

In accordance with the present invention, each of the dosage forms contains the same antibiotic; however, each of the dosage forms may contain more than one antibiotic.

In one embodiment, where the composition contains one immediate release component and two delayed release components, the immediate release component provides from 20% to 35% (preferably 20% to 30%), by weight, of the total antibiotic; where there is three delayed release components, the immediate release component provides from 15% to 30%, by weight, of the total antibiotic; and where there are four delayed release components, the immediate release component provides from 10% to 25%, by weight, of the total antibiotic.

With respect to the delayed release components, where there are two delayed release components, the first delayed release component (the one released earlier in time) provides from 30% to 60%, by weight, of the total antibiotic provided by the two delayed release components with the second delayed release component providing the remainder of the antibiotic.

Where there are three delayed release components, the earliest released component provides 20% to 35% by weight of the total antibiotic provided by the three delayed release components, the next in time delayed release component provides from 20% to 40%, by weight, of the antibiotic provided by the three delayed release components and the last in time providing the remainder of the antibiotic provided by the three delayed release components.

When there are four delayed release components, the earliest delayed release component provides from 15% to 30%, by weight, the next in time delayed release component provides from 15% to 30%, the next in time delayed release component provides from 20% to 35%, by weight, and the last in time delayed release component provides from 20% to 35%, by weight, in each case of the total antibiotic provided by the four delayed release components.

The Immediate Release Component

The immediate release portion of this system can be a mixture of ingredients that breaks down quickly after administration to release the antibiotic. This can take the form of either a discrete pellet or granule that is mixed in with, or compressed with, the other three components.

The materials to be added to the antibiotics for the immediate release component can be, but are not limited to, microcrystalline cellulose, corn starch, pregelatinized starch, potato starch, rice starch, sodium carboxymethyl starch, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, ethylcellulose, chitosan, hydroxychitosan, hydroxymethylatedchitosan, cross-linked chitosan, cross-linked hydroxymethyl chitosan, maltodextrin, mannitol, sorbitol, dextrose, maltose, fructose, glucose, levulose, sucrose, polyvinylpyrrolidone (PVP), acrylic acid derivatives (Carbopol, Eudragit, etc.), polyethylene glycols, such a low molecular weight PEGs (PEG2000-10000) and high molecular weight PEGs (Polyox) with molecular weights above 20,000 daltons.

It may be useful to have these materials present in the range of 1.0 to 60% (W/W).

In addition, it may be useful to have other ingredients in this system to aid in the dissolution of the drug, or the breakdown of the component after ingestion or administration. These ingredients can be surfactants, such as sodium lauryl sulfate, sodium monoglycerate, sorbitan monooleate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, glyceryl monostearate, glyceryl monooleate, glyceryl monobutyrate, one of the non-ionic surfactants such as the Pluronic line of

surfactants, or any other material with surface active properties, or any combination of the above.

These materials may be present in the rate of 0.05-15% (W/W).

The non-pH Sensitive Delayed Release Component

The components in this composition are the same immediate release unit, but with additional polymers integrated into the composition, or as coatings over the pellet or granule.

Materials that can be used to obtain a delay in release suitable for this component of the invention can be, but are not limited to, polyethylene glycol (PEG) with molecular weight above 4,000 daltons (Carbowax, Polyox), waxes such as white wax or bees wax, paraffin, acrylic acid derivatives (Eudragit), propylene glycol, and ethylcellulose.

Typically these materials can be present in the range of 0.5-25% (W/W) of this component.

The pH Sensitive (Enteric) Release Component

The components in this composition are the same as the immediate release component, but with additional polymers integrated into the composition, or as coatings over the pellet or granule.

The kind of materials useful for this purpose can be, but are not limited to, cellulose acetate pthalate, Eudragit L, and other pthalate salts of cellulose derivatives.

These materials can be present in concentrations from 4-20% (W/W).

Sustained Release Component

The components in this composition are the same as the immediate release component, but with additional polymers integrated into the composition, or as coatings over the pellet or granule.

The kind of materials useful for this purpose can be, but are not limited to, ethylcellulose,hydroxypropylmethylcellulose,hydroxypropylcellulose, hydroxyethylcellulose, carboxymethylcellulose, methylcellulose, nitrocellulose, Eudragit R, and Eudragit RL, Carbopol, or polyethylene glycols with molecular weights in excess of 8,000 daltons.

These materials can be present in concentrations from 4-20% (W/W).

As hereinabove indicated, the units comprising the antibiotic composition of the present invention can be in the form of discrete pellets or particles contained in the capsule, or particles embedded in a tablet or suspended in a liquid suspension.

The antibiotic composition of the present invention may be administered, for example, by any of the following routes of administration: sublingual, transmucosal, transdermal, parenteral, etc., and preferably is administered orally. The composition includes a therapeutically effective amount of the antibiotic, which amount will vary with the antibiotic to be used, the disease or infection to be treated, and the number of times that the composition is to be delivered in a day. The composition is administered to a host in an amount effective for treating a bacterial infection.

This system will be especially useful in extending the practial therapeutic activity for antibiotics with elimination half lives of less than 20 hours and more particularly with elimination half-lives of less than 12 hours, and will be particularly useful for those drugs with half-lives of 2-10 hours. The following are examples of some antibiotics with half-lives of about 1 to 12 hours: Cefadroxil, cefazolin, cephalexin, cephalothin, cephapirin, cephacelor, cephprozil, cephadrine, cefamandole, cefonicid, ceforanide, cefuroxime, cefixime, cefoperazone, cefotaxime, cefpodoxime, ceftaxidime, ceftibuten, ceftizoxime, ceftriaxone, cefepime, cefmetazole, cefotetan, cefoxitin, loracarbef, imipenem, erythromycin (and erythromycin salts such as estolate, ethylsuccinate, gluceptate, lactobionate, stearate), azithromycin,

clarithromycoin, dirithromycin, troleanomycin, penicillin V, peniciliin salts, and complexes, methicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin, amoxicillin, amoxicillin and clavulanate potassium, ampicillin, bacampicillin, carbenicillin indanyl sodium (and other salts of carbenicillin) mezlocillin, piperacillin, piperacillin and taxobactam, ticarcillin, ticarcillin and clavulanate potassium, clindamycin, vancomycin, novobiocin, aminosalicylic acid, capreomycin, cycloserine, ethambutol HCl and other salts, ethionamide, and isoniazid, ciprofloxacin, levofloxacin, lomefloxacin, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin, sulfacytine, suflamerazine, sulfamethazine, sulfamethixole, sulfasalazine, sulfisoxazole, sulfapyrizine, sulfadiazine, sulfmethoxazole, sulfapyridine, metronidazole, methenamine, fosfomycin, nitrofurantoin, trimethoprim, clofazimine, co-triamoxazole, pentamidine, and trimetrexate.

The invention will be further described with respect to the following examples; however, the scope of the invention is not limited thereby. All percentages in this specification, unless otherwise specified, are by weight.

Examples

Immediate Release Component

Formulate the composition by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a dry blend. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum over or forced-air oven. The product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

	Ingredient	Conc. (% W/W)
Example 1:		
	Amoxicillin	65% (W/W)
	Microcrystalline cellulose	20
	Povidone	10
	Croscarmellose sodium	5
Example 2:		
	Amoxicillin	55% (W/W)

Microcrystalline cellulose	25
Povidone	10
Croscarmellose sodium	10

Example 3:

Amoxicillin	65% (W/W)
Microcrystalline cellulose	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 4:

Amoxicillin	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Hydroxypropylcellulose	5

Example 5:

Amoxicillin	75% (W/W)
Polyethylene glycol 8000	20
Polyvinylpyrrolidone	5

Example 6:

Clarithromycin	65% (W/W)
Microcrystalline cellulose	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 7:

Clarithromycin	75% (W/W)
Microcrystalline cellulose	15
Hydroxypropylcellulose	5
Croscarmellose sodium	5

Example 8:

Clarithromycin	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Hydroxypropylcellulose	5

Example 9:

Clarithromycin	75% (W/W)
Polyethylene glycol 8000	20
Polyvinylpyrrolidone	5

Example 10:

Ciprofloxacin	65% (W/W)
Microcrystalline cellulose	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 11:

Ciprofloxacin	75% (W/W)
Microcrystalline cellulose	15
Hydroxypropylcellulose	5
Croscarmellose sodium	5

Example 12:

Ciprofloxacin	75% (W/W)
Polyethylene glycol 4000	10
Polytheylene glycol 2000	10
Hydroxypropylcellulose	5

Example 13:

Cirpofloxacin	75% (W/W)
Polyethylene glycol 8000	20
Polyvinylpyrrolidone	5

Example 14:

Ceftibuten	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Hydroxypropylcellulose	5

Example 15:

Ceftibuten	75% (W/W)
Polyethylene Glycol 4000	20
Polyvinylpyrrolidone	5

non-pH Sensitive Delayed Release Component

Formulate the composition by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum over or forced-air oven. Allow the product to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

	Ingredient	Conc. (% W/W)
Example 16:		
	Amoxicillin	65% (W/W)
	Microcrystalline cellulose	20
	Polyox	10
	Croscarmellose sodium	5

Example 17:

Amoxicillin	55% (W/W)
Microcrystalline cellulose	25
Polyox	10
Glyceryl monooleate	10

Example 18:

Amoxicillin	65% (W/W)
Polyox	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 19:

Amoxicillin	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Eudragit RL 30D	5

Example 20:

Amoxicillin	75% (W/W)
Polyethylene glycol 8000	20
Ethylcellulose	5

Example 21:

Clarithromycin	70% (W/W)
Polyox	20
Hydroxypropylcellulose	5
Croscarmellose sodium	5

Example 22:

Clarithromycin	75% (W/W)
Polyox	15
Hydroxypropylcellulose	5
Ethylcellulose	5

Example 23:

Clarithromycin	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Eudragit RL 30D	5

Example 24:

Clarithromycin	80% (W/W)
Polyethylene glycol 8000	10
Polyvinylpyrrolidone	5
Eudgragit R 30D	5

Example 25:

Ciprofloxacin	65% (W/W)
Polyethylene glycol 4000	20

	Hydroxypropylcellulose	10
	Eudragit RL 30D	5
Example 26:		
	Ciprofloxacin	75% (W/W)
	Microcrystalline cellulose	15
	Hydroxypropylcellulose	5
	Ethylcellulose	5
Example 27:		
	Ciprofloxacin	80% (W/W)
	Polyethylene glycol 4000	10
	Polyethylene glycol 2000	5
	Eudgragit RL 30D	5
Example 28:		
	Ciprofloxacin	75% (W/W)
	Polyethylene glycol 8000	20
	Ethylcellulose	5
Example 29:		
	Ceftibuten	75% (W/W)
	Polyethylene glycol 4000	10
	Polyethylene glycol 2000	10
	Eudragit RL 30D	5
Example 30:		
	Ceftibuten	75% (W/W)
	Polyethylene glycol 8000	20
	Ethylcellulose	5

Enteric Release Component

Formulate the ingredients by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum over or forced-air oven. Allow the product to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

	Ingredient	Conc. (% W/W)
Example 31:		
	Amoxicillin	65% (W/W)
	Microcrystalline cellulose	20

Cellulose Acetate Pthalate	15

Example 32:

Amoxicillin	55% (W/W)
Microcrystalline cellulose	25
Cellulose Acetate Pthalate	10
Hydroxypropylmethylcellulose	10

Example 33:

Amoxicillin	65% (W/W)
Polyox	20
Hydroxypropylcellulose pthalate	10
Eudragit L30D	5

Example 34:

Amoxicillin	75% (W/W)
Polyethylene glycol 2000	10
Eudragit L30D	10
Eudragit RL 30D	5

Example 35:

Amoxicillin	40% (W/W)
Microcrystalline Cellulose	40
Cellulose Acetate Pthalate	10

Example 36:

Clarithromycin	70% (W/W)
Hydroxypropylcellulose pthalate	15
Croscarmellose sodium	10

Example 37:

Clarithromycin	70% (W/W)
Eudragit E30D	15
Hydroxypropylcellulose	10
Ethylcellulose	5

Example 38:

Clarithromycin	75% (W/W)
Polyethylene glycol 2000	10
Eudragit E 30D	15

Example 39:

Clarithromycin	40% (W/W)
Lactose	50
Eudgragit L 30D	10

Example 40:

Ciprofloxacin	65% (W/W)
Microcrystalline Cellulose	20
Eudragit L 30D	10

Example 41:

Ciprofloxacin	75% (W/W)
Microcrystalline Cellulose	15
Hydroxypropylcellulose pthalate	10

Example 42:

Ciprofloxacin	80% (W/W)
Lactose	10
Eudgragit L 30D	10

Example 43:

Ciprofloxacin	70% (W/W)
Polyethylene glycol 4000	20
Cellulose acetate pthalate	10

Example 44:

Ceftibuten	60% (W/W)
Polyethylene glycol 2000	10
Lactose	20
Eudragit L 30D	10

Example 45:

Ceftibuten	70% (W/W)
Microcrystalline cellulose	20
Cellulose acetate pthalate	10

Sustained Release Component

Formulate the composition by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum over or forced-air oven. Allow the product to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

	Ingredient	Conc. (% W/W)
Example 46:		
	Amoxicillin	65% (W/W)
	Ethylcellulose	20
	Polyox	10
	Hydroxypropylmethylcellulose	5

Example 47:

Amoxicillin	55% (W/W)
Lactose	25
Polyox	10
Glyceryl monooleate	10

Example 48:

Amoxicillin	70% (W/W)
Polyox	20
Hydroxypropylcellulose	10

Example 49:

Clarithromycin	75% (W/W)
Lactose	15
Hydroxypropylcellulose	5
Ethylcellulose	5

Example 50:

Clarithromycin	75% (W/W)
Polyethylene glycol 4000	10
Lactose	10
Eudragit RL 30D	5

Example 51:

Clarithromycin	80% (W/W)
Polyethylene glycol 8000	10
Hydroxypropylmethylcellulose	5
Eudgragit RS 30D	5

Example 52:

Ciprofloxacin	75% (W/W)
Hydroxyethylcellulose	10
Polyethylene glycol 4000	10
Hydroxypropylcellulose	5

Example 53:

Ciprofloxacin	75% (W/W)
Lactose	10
Povidone (PVP)	10
Polyethylene glycol 2000	5

Example 54:

Ceftibuten	75% (W/W)
Polyethylene glycol 4000	10
Povidone (PVP)	10
Hydroxypropylcellulose	5

Example 55:

Ceftibuten	75% (W/W)
Lactose	15

Polyethylene glycol 4000	5
Polyvinylpyrrolidone	5

Three Pulses

Example 56.

1. Metronidazole Matrix Pellet Formulation and Preparation Procedure (Immediate Release)

A. Pellet Formulation

The composition of the metronidazole matrix pellets provided in Table 1.

Table 1 Composition of Metronidazole Pellets

Component	Percentage (%)
Metronidazole	50
Avicel PH 101	20
Lactose	20
PVP K29/32*	10
Purified Water	
Total	100

*PVP K29/32 was added as a 20% w/w aqueous solution during wet massing.

B. Preparation Procedure for Metronidazole Matrix Pellets

1.2.1 Blend metronidazole and Avicel® PH 101 using a Robot Coupe high shear granulator.

1.2.2 Add 20% Povidone K29/32 binder solution slowly into the powder blend under continuous mixing.

1.2.3 Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator was 1.0 mm.

1.2.4 Spheronize the extrudate using a Model SPH20 Caleva Spheronizer.

1.2.5 Dry the spheronized pellets at 50°C overnight.

1.2.6 Pellets between 16 and 30 Mesh were collected for further processing.

1.3 Preparation of an Eudragit® L 30 D-55 Aqueous Coating Dispersion

A. Dispersion Formulation

The composition of the aqueous Eudragit L30D-55 dispersion applied to the metronidazole matrix pellets is provided below in Table 2.

Table 2 Eudragit® L 30 D-55 Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30 D-55	55.0
Triethyl Citrate	1.6
Talc	8.0
Purified Water	37.4
Solids Content	25.5
Polymer Content	15.9

B. Preparation Procedure for an Eudragit® L 30 D-55 Aqueous Dispersion

1.3.1 Suspend triethyl citrate and talc in deionized water.

1.3.2 The TEC/talc suspension is then homogenized using a PowerGen 700 high shear mixer.

1.3.3 Add the TEC/talc suspension slowly to the Eudragit® L 30 D-55 latex dispersion while stirring.

1.3.4 Allow the coating dispersion to stir for one hour prior to application onto the metronidazole matrix pellets.

1.4 Preparation of an Eudragit® S 100 Aqueous Coating Dispersion

A. Dispersion Formulation

The composition of the aqueous Eudragit® S 100 dispersion applied to the metronidazole matrix pellets is provided below in Table 3.

Table 3 Eudragit® S 100 Aqueous Coating Dispersion

Component	Percentage (%)
Part A	
Eudragit® S 100	12.0
1 N Ammonium Hydroxide	6.1
Triethyl Citrate	6.0
Purified Water	65.9
Part B	
Talc	2.0
Purified Water	8.0
Solid Content	20.0
Polymer Content	12.0

B. Preparation Procedure for an Eudragit® S 100 Aqueous Dispersion

Part I:

(i) Dispense Eudragit® S 100 powder in deionized water with stirring.

(ii) Add ammonium hydroxide solution drop-wise into the dispersion with stirring.

(iii) Allow the partially neutralized dispersion to stir for 60 minutes.

(iv) Add triethyl citrate drop-wise into the dispersion with stirring. Stir for about 2 hours prior to the addition of Part B.

Part II:

(i) Disperse talc in the required amount of water

(ii) Homogenize the dispersion using a PowerGen 700D high shear mixer.

(iii) Part B is then added slowly to the polymer dispersion in Part A with a mild stirring.

1.5 Coating Conditions for the Application of Aqueous Coating Dispersions

The following coating parameters were used to coat matrix pellets with each of the Eudragit® L 30 D-55 and Eudragit® S 100 aqueous film coating.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	40 to 45 °C
Outlet Air Temperature	30 to 33 °C
Atomization Air Pressure	1.8 Bar
Pump Rate	2 gram per minute

(i) Coat matrix pellets with L30 D-55 dispersion such that you apply 12% coat weight gain to the pellets.

(ii) Coat matrix pellets with S100 dispersion such that you apply 20% coat weight gain to the pellets.

1.6 Encapsulation of the Metronidazole Pellets

Pellets are filled into size 00 hard gelatin capsules at a ratio of 30%: 30%: 40%: Immediate-release matrix pellets uncoated, L30 D-55 coated pellets and S100 coated pellets respectively.

The capsule is filled with the three different pellets to achieve a total dose of 375mg/capsule.

Three Pulses

Example 57

Amoxicillin Pellet Formulation and Preparation Procedure

57.1 Pellet Formulations for subsequent coating

The composition of the Amoxicillin trihydrate matrix pellets provided in Table 4.

Table 4 Composition of Amoxicillin Matrix Pellets

Component	Percentage (%)
Amoxicillin Trihydrate powder	92
Avicel PH 101	7.0
Hydroxypropyl methylcellulose, NF*	1.0
Total	100

*Hydroxypropyl methylcellulose was added as a 2.9% w/w aqueous solution during wet massing.

57.2 Preparation Procedure for Amoxicillin Matrix Pellets

57.2.1 Blend Amoxicillin and Avicel® PH 101 using a low shear blender.

57.2.2 Add the hydroxypropyl methylcellulose binder solution slowly into the powder blend under continuous mixing.

57.2.3 Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator is 0.8 mm.

57.2.4 Spheronize the extrudate using a QJ-230 Spheronizer using a small cross section plate.

57.2.5 Dry the spheronized pellets at 60°C using a fluid bed dryer until the exhaust temperature reaches 40°C.

57.2.6 Pellets between 20 and 40 Mesh were collected for further processing.

57.3 Preparation of an Eudragit® L 30 D-55 Aqueous Coating Dispersion

57.3.1 Dispersion Formulation

The composition of the aqueous Eudragit L30D-55 dispersion applied to the amoxicillin matrix pellets is provided below in Table 5.

Table 5 Eudragit® L 30 D-55 Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30 D-55	41.6
Triethyl Citrate	2.5
Talc	5.0
Purified Water	50.9
Solids Content	20.0
Polymer Content	12.5

57.4 Preparation Procedure for an Eudragit® L 30 D-55 Aqueous Dispersion

57.4.1 Suspend triethyl citrate and talc in deionized water.

57.4.2 The TEC/talc suspension is mixed using laboratory mixer.

57.4.3 Add the TEC/talc suspension from slowly to the Eudragit® L 30 D-55 latex dispersion while stirring.

57.4.4 Allow the coating dispersion to stir for one hour prior to application onto the amoxicillin matrix pellets.

57.5 Preparation of an Eudragit® S 100 Aqueous Coating Dispersion

57.5.1 Dispersion Formulation

The composition of the aqueous Eudragit® S 100 dispersion applied to the Amoxicillin matrix pellets is provided below in Table 6.

Table 6 Eudragit® S 100 Aqueous Coating Dispersion

Component	Percentage (%)
Part A	
Eudragit® S 100	10.0
1 N Ammonium Hydroxide	5.1
Triethyl Citrate	5.0
Water	64.9
Part B	
Talc	5.0
Water	10.0
Solid Content	25.0
Polymer Content	10.0

57.6 Preparation Procedure for an Eudragit® S 100 Aqueous Dispersion

Part A:

57.6.1 Dispense Eudragit® S 100 powder in deionized water with stirring.

57.6.2 Add ammonium hydroxide solution drop-wise into the dispersion with stirring.

57.6.3 Allow the partially neutralized dispersion to stir for 60 minutes.

57.6.4 Add triethyl citrate drop-wise into the dispersion with stirring and let stir overnight prior to the addition of Part B.

Part B:

57.6.5 Disperse talc in the required amount of water

57.6.6 Stir the dispersion using an overhead laboratory mixer.

57.6.7 Part B is then added slowly to the polymer dispersion in Part A with a mild stirring.

57.7 Coating Conditions for the Application of Aqueous Coating Dispersions

The following coating parameters were used for both the Eudragit® L 30 D-55 and Eudragit® S 100 aqueous film coating processes.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	40 to 45 °C
Outlet Air Temperature	30 to 33 °C
Atomization Air Pressure	1.8 Bar
Pump Rate	2-6 gram per minute

57.7.1 Coat matrix pellets with L30 D-55 dispersion such that you apply 20% coat weight gain to the pellets.

57.7.2 Coat matrix pellets with S100 dispersion such that you apply 37% coat weight gain to the pellets.

57.8 Preparation of Amoxicillin Granulation (Immediate Release Component) for tabletting

Table 7 Composition of Amoxicillin Granulation

Component	Percentage (%)
Amoxicillin Trihydrate powder	92
Avicel PH 101	7.0

Hydroxypropyl methylcellulose, NF*	1.0
Total	100

*Hydroxypropyl methylcellulose was added as a 2.9% w/w aqueous solution during wet massing.

57.8.1 Blend Amoxicillin and Avicel® PH 101 using a low shear blender.

57.8.2 Add the hydroxypropyl methylcellulose binder solution slowly into the powder blend under continuous mixing.

57.8.3 Dry the granulation at 60°C using a fluid bed dryer until the exhaust temperature reaches 40°C.

57.8.4 Granules between 20 and 40 Mesh are collected for further processing.

57.9 Tabletting of the Amoxicillin Pellets

Table 8 Composition of Amoxicillin Tablets

Component	Percentage (%)
Amoxicillin granules	32.5
Avicel PH 200	5.0
Amoxicillin L30D-55 coated pellets	30
Amoxicillin S100 coated pellets	30
Colloidal silicon dioxide	1.5
Magnesium stearate	1.0
Total	100

57.9.1 Blend the Amoxicillin granules, Avicel PH-200, Amoxicillin pellets and colloidal silicon dioxide for 15 minutes in a tumble blender.

57.9.2 Add the magnesium stearate to the blender, and blend for 5 minutes.

57.9.3 Compress the blend on a rotary tablet press.

57.9.4 The fill weight should be adjusted to achieve a 500 mg dose tablet.

Three Pulses

Example 58

Clarithromycin Pellet Formulation and Preparation Procedure

58.1 Pellet Formulation

The composition of the clarithromycin matrix pellets provided in Table 1.

Table 9 Composition of Clarithromycin Pellets

Component	Percentage (%)
Clarithromycin	50.6
Lactose monohydrate, spray dried	32.1
Silicified microcrystalline cellulose	14.6
Polyoxyl 35 Castor Oil*	1.7
Hydroxypropyl methylcellulose*	1.0
Total	100

*Hydroxypropyl methylcellulose and Polyoxyl 35 were added as an 8.7% w/w aqueous solution during wet massing.

58.2 Preparation Procedure for Clarithromycin Matrix Pellets

58.2.1 Blend clarithromycin, silicified microcrystalline cellulose and lactose monohydrate using a Robot Coupe high shear granulator.

58.2.2 Prepare the binder solution by adding the Polyoxyl to the purified water while stirring. After that is mixed, slowly add the hydroxypropyl methylcellulose and continue to stir until a solution is achieved.

58.2.3 Add binder solution slowly into the powder blend under continuous mixing.

58.2.4 Granulate the powders in the high shear granulator with the binder solution.

58.2.5 Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator was 1.2 mm.

58.2.6 Spheronize the extrudate using a Model SPH20 Caleva Spheronizer.

58.2.7 Dry the spheronized pellets at 50°C overnight.

58.2.8 Pellets between 18 and 30 Mesh were collected for further processing.

58.3 Preparation of an Eudragit® L 30 D-55 Aqueous Coating Dispersion

58.3.1 Dispersion Formulation

The composition of the aqueous Eudragit L30D-55 dispersion applied to the clarithromycin matrix pellets is provided below in Table 10.

Table 10 Eudragit® L 30 D-55 Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30 D-55	40.4
Triethyl Citrate	1.8
Talc	6.1
Water	51.7
Solids Content	20.0
Polymer Content	12.1

58.4 Preparation Procedure for an Eudragit® L 30 D-55 Aqueous Dispersion

58.4.1 Suspend triethyl citrate and talc in deionized water.

58.4.2 The TEC/talc suspension is then homogenized using a PowerGen 700 high shear mixer.

58.4.3 Add the suspension from 4.2.2 slowly to the Eudragit® L 30 D-55 latex dispersion while stirring.

58.4.4 Allow the coating dispersion to stir for one hour prior to application onto the clarithromycin matrix pellets.

58.5 Preparation of an Eudragit® S 100 Aqueous Coating Dispersion

58.5.1 Dispersion Formulation

The composition of the aqueous Eudragit® S 100 dispersion applied to the clarithromycin matrix pellets is provided below in Table 11.

Table 11 Eudragit® S 100 Aqueous Coating Dispersion

Component	Percentage (%)
Part A	
Eudragit® S 100	10.0
1 N Ammonium Hydroxide	5.1
Triethyl Citrate	5.0
Water	64.9
Part B	
Talc	5.0
Water	10.0
Solid Content	25.0
Polymer Content	10.0

58.6 Preparation Procedure for an Eudragit® S 100 Aqueous Dispersion

Part A:

58.6.1 Dispense Eudragit® S 100 powder in deionized water with stirring.

58.6.2 Add ammonium hydroxide solution drop-wise into the dispersion with stirring.

58.6.3 Allow the partially neutralized dispersion to stir for 60 minutes

58.6.4 Add the triethyl citrate drop-wise to the dispersion and stir for 60 minutes prior to the addition of Part B.

Part B:

58.6.5 Disperse talc in the required amount of water

58.6.6 Homogenize the dispersion using a PowerGen 700D high shear mixer.

58.6.7 Part B is then added slowly to the polymer dispersion in Part A with a mild stirring.

58.7 Coating Conditions for the Application of Aqueous Coating Dispersions

The following coating parameters were used for coating the matrix pellets with each of the Eudragit® L 30 D-55 and Eudragit® S 100 aqueous film coating.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	40 to 45 °C
Outlet Air Temperature	30 to 33 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	2 gram per minute

58.7.1 Coat matrix pellets with L30 D-55 dispersion such that you apply 20% coat weight gain to the pellets.

58.7.2 Coat matrix pellets with S100 dispersion such that you apply 37% coat weight gain to the pellets.

4. Capsules were filled with the uncoated pellets, the L30D-55 coated pellets and S100 coated pellets in weight percentages of 30%:30%:40%, respectively to provide 250 mg. capsules.

Four pulses

Example 59.

1 Metronidazole Matrix Pellet Formulation and Preparation Procedure

59.1 Pellet Formulation

The composition of the metronidazole matrix pellets provided in Table 12.

Table 12 Composition of Metronidazole Pellets

Component	Percentage (%)
Metronidazole	50
Avicel PH 101	20
Lactose	20
PVP K29/32*	10
Purified Water	
Total	100

*PVP K29/32 was added as a 20% w/w aqueous solution during wet massing.

59.2 Preparation Procedure for Metronidazole Matrix Pellets

59.2.1 Blend metronidazole and Avicel® PH 101 using a Robot Coupe high shear granulator.

59.2.2 Add 20% Povidone K29/32 binder solution slowly into the powder blend under continuous mixing.

59.2.3 Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator was 1.0 mm.

59.2.4 Spheronize the extrudate using a Model SPH20 Caleva Spheronizer.

59.2.5 Dry the spheronized pellets at 50°C overnight.

59.2.6 Pellets between 16 and 30 Mesh were collected for further processing.

59.3 Preparation of an Eudragit® L 30 D-55 Aqueous Coating Dispersion

59.3.1 Dispersion Formulation

The composition of the aqueous Eudragit L30D-55 dispersion applied to the metronidazole matrix pellets is provided below in Table 13.

Table 13 Eudragit® L 30 D-55 Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30 D-55	55.0
Triethyl Citrate	1.6
Talc	8.0
Purified Water	37.4
Solids Content	25.5
Polymer Content	15.9

59.4 Preparation Procedure for an Eudragit® L 30 D-55 Aqueous Dispersion

59.4.1 Suspend triethyl citrate and talc in deionized water.

59.4.2 The TEC/talc suspension is then homogenized using a PowerGen 700 high shear mixer.

59.4.3 Add the TEC/talc suspension slowly to the Eudragit® L 30 D-55 latex dispersion while stirring.

59.4.4 Allow the coating dispersion to stir for one hour prior to application onto the metronidazole matrix pellets.

59.5 Preparation of an Eudragit® S 100 Aqueous Coating Dispersion

59.5.1 Dispersion Formulation

The composition of the aqueous Eudragit® S 100 dispersion applied to the metronidazole matrix pellets is provided below in Table 14.

Table 14 Eudragit® S 100 Aqueous Coating Dispersion

Component	Percentage (%)
Part A	
Eudragit® S 100	12.0
1 N Ammonium Hydroxide	6.1
Triethyl Citrate	6.0
Purified Water	65.9
Part B	
Talc	2.0
Purified Water	8.0
Solid Content	20.0
Polymer Content	12.0

59.6 Preparation Procedure for an Eudragit® S 100 Aqueous Dispersion

Part A:

59.6.1 Dispense Eudragit® S 100 powder in deionized water with stirring.

59.6.2 Add ammonium hydroxide solution drop-wise into the dispersion with stirring.

59.6.3 Allow the partially neutralized dispersion to stir for 60 minutes.

59.6.4 Add triethyl citrate drop-wise into the dispersion with stirring. Stir for about 2 hours prior to the addition of Part B.

Part B:

59.6.5 Disperse talc in the required amount of water

59.6.6 Homogenize the dispersion using a PowerGen 700D high shear mixer.

59.6.7 Part B is then added slowly to the polymer dispersion in Part A with a mild stirring.

59.7 Coating Conditions for the Application of Aqueous Coating Dispersions

The following coating parameters were used for coating with each of the Eudragit® L 30 D-55 and Eudragit® S 100 aqueous film coatings.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	40 to 45 °C
Outlet Air Temperature	30 to 33 °C
Atomization Air Pressure	1.8 Bar
Pump Rate	2 gram per minute

59.7.1 Coat matrix pellets with L30 D-55 dispersion such that you apply 12% coat weight gain to the pellets.

59.7.2 Coat matrix pellets with L30 D-55 dispersion such that you apply 30% coat weight gain to the pellets.

59.7.3 Coat matrix pellets with S100 dispersion such that you apply 20% coat weight gain to the pellets.

59.8 Encapsulation of the Metronidazole Pellets

Pellets are filled into size 00 hard gelatin capsules at a ratio of 20%: 30%: 20%: 30% Immediate-release matrix pellets (uncoated), L30 D-55 coated pellets 12% weight gain, L30D-55 coated pellets 30% weight gain and S100 coated pellets respectively. The capsule is filled with the four different pellets to achieve a total dose of 375mg/capsule.

Four Pulses

Example 60

Amoxicillin Pellet Formulation and Preparation Procedure

60.1 Pellet Formulations

The composition of the Amoxicillin trihydrate matrix pellets provided in Table 15.

Table 15 Composition of Amoxicillin Matrix Pellets

Component	Percentage (%)
Amoxicillin Trihydrate powder	92
Avicel PH 101	7.0
Hydroxypropyl methylcellulose, NF*	1.0
Total	100

*Hydroxypropyl methylcellulose was added as a 2.9% w/w aqueous solution during wet massing.

60.2 Preparation Procedure for Amoxicillin Matrix Pellets

60.2.1 Blend Amoxicillin and Avicel® PH 101 using a low shear blender.

60.2.2 Add the hydroxypropyl methylcellulose binder solution slowly into the powder blend under continuous mixing.

60.2.3 Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator is 0.8 mm.

60.2.4 Spheronize the extrudate using a QJ-230 Spheronizer using a small cross section plate.

60.2.5 Dry the spheronized pellets at 60°C using a fluid bed dryer until the exhaust temperature reaches 40°C.

60.2.6 Pellets between 20 and 40 Mesh were collected for further processing.

60.3 Preparation of an Eudragit® L 30 D-55 Aqueous Coating Dispersion

60.3.1 Dispersion Formulation

The composition of the aqueous Eudragit L30D-55 dispersion applied to the amoxicillin matrix pellets is provided below in Table 16.

Table 16 Eudragit® L 30 D-55 Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30 D-55	41.6
Triethyl Citrate	2.5
Talc	5.0
Purified Water	50.9
Solids Content	20.0
Polymer Content	12.5

60.4 Preparation Procedure for an Eudragit® L 30 D-55 Aqueous Dispersion

60.4.1 Suspend triethyl citrate and talc in deionized water.

60.4.2 The TEC/talc suspension is mixed using laboratory mixer.

60.4.3 Add the TEC/talc suspension from slowly to the Eudragit® L 30 D-55 latex dispersion while stirring.

60.4.4 Allow the coating dispersion to stir for one hour prior to application onto the amoxicillin matrix pellets.

60.5 Preparation of an Eudragit® S 100 Aqueous Coating Dispersion

60.6 Dispersion Formulation

The composition of the aqueous Eudragit® S 100 dispersion applied to the Amoxicillin matrix pellets is provided below in Table 17.

Table 17 Eudragit® S 100 Aqueous Coating Dispersion

Component	Percentage (%)
Part A	
Eudragit® S 100	10.0
1 N Ammonium Hydroxide	5.1
Triethyl Citrate	5.0
Water	64.9
Part B	
Talc	2.0
Water	10.0
Solid Content	25.0
Polymer Content	10.0

60.7 Preparation Procedure for an Eudragit® S 100 Aqueous Dispersion

Part A:

60.7.1 Dispense Eudragit® S 100 powder in deionized water with stirring.

60.7.2 Add ammonium hydroxide solution drop-wise into the dispersion with stirring.

60.7.3 Allow the partially neutralized dispersion to stir for 60 minutes.

60.7.4 Add triethyl citrate drop-wise into the dispersion with stirring and let stir overnight prior to the addition of Part B.

Part B:

60.7.5 Disperse talc in the required amount of water

60.7.6 Stir the dispersion using an overhead laboratory mixer.

60.7.7 Part B is then added slowly to the polymer dispersion in Part A with a mild stirring.

60.8 Preparation of Aquacoat Coating Dispersion

60.8.1 Dispersion Formulation

The composition of the aqueous Aquacoat dispersion applied to Amoxicillin L30 D-55 coated pellets is provided below in Table 18.

Table 18

Component	Percentage (%)
Aquacoat ECD	79.3
Hydroxypropyl methylcellulose	15.9
Dibutyl Sebacate	4.8
Purified Water (300g)	

60.8.1.1 Prepare Hydroxypropyl methylcellulose (Methocel E15) solution by dispersing in water with continuous stirring.

60.8.1.2 Add Aquacoat and dibutyl sebacate to the dispersion with stirring and continue to stir overnight.

60.9 Coating Conditions for the Application of Aqueous Coating Dispersions

The following coating parameters were used for coating with each of the Eudragit® L 30 D-55 and Eudragit® S 100 aqueous film coatings.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	40 to 45 °C
Outlet Air Temperature	30 to 33 °C
Atomization Air Pressure	1.8 Bar
Pump Rate	2-6 gram per minute

60.9.1 Coat Amoxicillin matrix pellets with L30 D-55 dispersim to achieve a 20% coat weight gain.

60.9.2 Coat another batch of Amoxicillin matrix pellets with L30 D-55 dispersion to achieve a 20% weight gain. Coat the L30 D-55 pellets with the Aquacoat Dispersion to achieve a 10% coat weight gain.

60.9.3 Coat Amoxicillin matrix pellets with S100 dispersion to achieve a 37% coat weight gain.

60.10 Preparation of Amoxicillin Granulation for tabletting

Table 19 Composition of Amoxicillin Granulation (Immediate Release)

Component	Percentage (%)
Amoxicillin Trihydrate powder	92
Avicel PH 101	7.0
Hydroxypropyl methylcellulose, NF*	1.0
Total	100

*Hydroxypropyl methylcellulose was added as a 2.9% w/w aqueous solution during wet massing.

60.10.1 Blend Amoxicillin and Avicel® PH 101 using a low shear blender.

60.10.2 Add the hydroxypropyl methylcellulose binder solution slowly into the powder blend under continuous mixing.

60.10.3 Dry the granulation at 60°C using a fluid bed dryer until the exhaust temperature reaches 40°C.

60.10.4 Granules between 20 and 40 Mesh are collected for further processing.

60.11 Tabletting of the Amoxicillin Pellets

Table 20 Composition of Amoxicillin Tablets

Component	Percentage (%)

Amoxicillin granules	32.5
Avicel PH 200	5.0
Amoxicillin L30D-55 coated pellets	20
Amoxicillin Aquacoated pellets	20
Amoxicillin S100 coated pellets	20
Colloidal silicon dioxide	1.5
Magnesium stearate	1.0
Total	100

60.11.1 Blend the Amoxicillin granules, Avicel PH-200, Amoxicillin pellets and colloidal silicon dioxide for 15 minutes in a tumble blender.

60.11.2 Add the magnesium stearate to the blender, and blend for 5 minutes.

60.11.3 Compress the blend on a rotary tablet press.

60.11.4 The fill weight should be adjusted to achieve a 500 mg dose tablet.

Four Pulses

Example 61

Clarithromycin Pellet Formulation and Preparation Procedure

61.1 Pellet Formulation

The composition of the clarithromycin matrix pellets provided in Table 21.

Table 21 Composition of Clarithromycin Pellets

Component	Percentage (%)
Clarithromycin	50.6
Lactose monohydrate, spray dried	32.1
Silicified microcrystalline cellulose	14.6
Polyoxyl 35 Castor Oil*	1.7
Hydroxypropyl methylcellulose*	1.0
Total	100

*Hydroxypropyl methylcellulose and Polyoxyl 35 were added as an 8.7% w/w aqueous solution during wet massing.

61.2 Preparation Procedure for Clarithromycin Matrix Pellets

61.2.1 Blend clarithromycin, silicified microcrystalline cellulose and lactose monohydrate using a Robot Coupe high shear granulator.

61.2.2 Prepare the binder solution by adding the Polyoxyl to the purified water while stirring. After that is mixed, slowly add the

hydroxypropyl methylcellulose and continue to stir until a solution is achieved.

61.2.3 Add binder solution slowly into the powder blend under continuous mixing.

61.2.4 Granulate the powders in the high shear granulator with the binder solution.

61.2.5 Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator was 1.2 mm.

61.2.6 Spheronize the extrudate using a Model SPH20 Caleva Spheronizer.

61.2.7 Dry the spheronized pellets at 50°C overnight.

61.2.8 Pellets between 18 and 30 Mesh were collected for further processing.

61.3 Preparation of an Eudragit® L 30 D-55 Aqueous Coating Dispersion

61.3.1 Dispersion Formulation

The composition of the aqueous Eudragit L30D-55 dispersion applied to the clarithromycin matrix pellets is provided below in Table 22.

Table 22 Eudragit® L 30 D-55 Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30 D-55	40.4
Triethyl Citrate	1.8
Talc	6.1
Water	51.7
Solids Content	20.0
Polymer Content	12.1

61.4 Preparation Procedure for an Eudragit® L 30 D-55 Aqueous Dispersion

61.4.1 Suspend triethyl citrate and talc in deionized water.

61.4.2 The TEC/talc suspension is then homogenized using a PowerGen 700 high shear mixer.

61.4.3 Add the suspension from 4.2.2 slowly to the Eudragit® L 30 D-55 latex dispersion while stirring.

61.4.4 Allow the coating dispersion to stir for one hour prior to application onto the clarithromycin matrix pellets.

61.5 Preparation of an Eudragit® S 100 Aqueous Coating Dispersion

61.5.1 Dispersion Formulation

The composition of the aqueous Eudragit® S 100 dispersion applied to the clarithromycin matrix pellets is provided below in Table 23.

Table 23 Eudragit® S 100 Aqueous Coating Dispersion

Component	Percentage (%)
Part A	
Eudragit® S 100	10.0
1 N Ammonium Hydroxide	5.1
Triethyl Citrate	5.0
Water	64.9
Part B	
Talc	5.0
Water	10.0
Solid Content	25.0
Polymer Content	10.0

61.6 Preparation Procedure for an Eudragit® S 100 Aqueous Dispersion

Part A:

61.6.1 Dispense Eudragit® S 100 powder in deionized water with stirring.

61.6.2 Add ammonium hydroxide solution drop-wise into the dispersion with stirring.

61.6.3 Allow the partially neutralized dispersion to stir for 60 minutes

61.6.4 Add the triethyl citrate drop-wise to the dispersion and stir for 60 minutes prior to the addition of Part B.

Part B:

61.6.5 Disperse talc in the required amount of water

61.6.6 Homogenize the dispersion using a PowerGen 700D high shear mixer.

61.6.7 Part B is then added slowly to the polymer dispersion in Part A with a mild stirring.

61.7 Coating Conditions for the Application of Aqueous Coating Dispersions

The following coating parameters were used for coating with each of the Eudragit® L 30 D-55 and Eudragit® S 100 aqueous film coatings.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	40 to 45 °C
Outlet Air Temperature	30 to 33 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	2 gram per minute

61.7.1 Coat matrix pellets with L30 D-55 dispersion such that you apply 12% coat weight gain to the pellets.

61.7.2 Coat matrix pellets with L30 D-55 dispersion such that you apply 30% coat weight gain to the pellets.

61.7.3 Coat matrix pellets with S100 dispersion such that you apply 37% coat weight gain to the pellets.

61.8 Encapsulation of the Clarithromycin Pellets

Pellets are filled into size 00 hard gelatin capsules at a ratio of 20%: 30%: 20%: 30% Immediate-release matrix pellets (uncoated), L30 D-55 coated pellets 12% weight gain, L30D-55 coated pellets 30% weight gain and S100 coated pellets respectively. The capsule is filled with the four different pellets to achieve a total dose of 250mg/capsule.

Four pulses

Example 62.

Levofloxacin Pellet Formulation and Preparation Procedure

Pellet Formulation

The composition of the Levofloxacin pellets provided in Table 1.

Table 1 Composition of Levofloxacin Pellets

Component	Percentage (%)
Levofloxacin	93
Avicel PH 101	3
Methocel E5P LV	4
Purified Water	*
Total	100

*Removed during processing

Preparation Procedure for Levofloxacin Pellets

- Blend Levofloxacin, Avicel® PH 101, and Methocel using a Robot Coupe high shear granulator.
- Add the purified water slowly into the powder blend under continuous mixing.
- Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator was 1.0 mm.

- Spheronize the extrudate using a Model SPH20 Caleva Spheronizer.

- Dry the spheronized pellets at 50°C until moisture level is < 3%.

- Pellets between 16 and 30 Mesh were collected for further processing.

Levofloxacin Enteric-Release Pellet Formulation and Preparation Procedure

Preparation of an Eudragit® L 30 D-55 Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit L30D-55 coating dispersion applied to the Levofloxacin pellets is provided below in Table 2.

Table 2 Eudragit® L 30 D-55 Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30 D-55	55.0
Triethyl Citrate	1.6
Talc	8.0
Purified Water*	37.4
Solids Content	25.5
Polymer Content	15.9

*Removed during processing

Preparation Procedure for an Eudragit® L 30 D-55 Aqueous Dispersion

Suspend triethyl citrate and talc in deionized water.

The TEC/talc suspension is then homogenized using a PowerGen 700 high shear mixer.

Add the TEC/talc suspension slowly to the Eudragit® L 30 D-55 latex dispersion while stirring.

Allow the coating dispersion to stir for one hour prior to application onto the Levofloxacin pellets.

Coating Conditions for the Application of Eudragit L30D-55 Aqueous Coating Dispersion

The following coating parameters were used for coating of the Eudragit® L 30 D-55 film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	40 to 45 °C
Outlet Air Temperature	30 to 33 °C
Atomization Air Pressure	1.8 Bar
Pump Rate	2 gram per minute

- Coat Levofloxacin pellets with Eudragit L30 D-55 film coating dispersion such that you apply 12% coat weight gain to the pellets.

Levofloxacin Delayed Enteric-Release Pellet Formulation and Preparation Procedure

Preparation of an Opadry Clear Coating Solution

Dispersion Formulation

The composition of the aqueous Opadry solution applied to the Levofloxacin pellets is provided below in Table 3.

Table 3 Opadry Clear Aqueous Coating Solution

Component	Percentage (%)
Opadry Clear YS-1-7006	7.0
Purified Water*	93.0
Solid Content %	7.0
Polymer Content %	7.0

*Removed during processing

Preparation Procedure for Opadry Clear Aqueous Solution

- Charge the purified water into a container
- Slowly add the Opadry Clear YS-1-7006 to the water with continuous mixing.

Preparation of an AQOAT AS-HF/Eudragit® FS30D Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous AQOAT AS-HF/ Eudragit FS30D coating dispersion applied to the Opadry coated Levofloxacin pellets is provided below in Table 4.

Table 4 AQOAT AS-HF/ Eudragit FS 30D Coating Dispersion

Component	Percentage (%)
AQOAT AS-HF	5.25
Eudragit FS30D	5.83
Triethyl Citrate	1.96
Sodium Lauryl Sulfate	0.21
Talc	2.10
Purified Water*	84.65
Solid Content	11.27
Polymer Content	7.0

*Removed during processing

Preparation Procedure for AQOAT AS-HF/ Eudragit FS30D Aqueous Dispersion

- Disperse triethyl citrate in purified water with stirring.
- Slowly add sodium lauryl sulfate into the triethyl citrate dispersion with stirring.
- Slowly add the AQOAT AS-HF powder to the dispersion above and stir for a minimum of 30 minutes.
- Slowly add the Eudragit FS30D dispersion to the AQOAT AS-HF dispersion and continue to stir for a minimum of 1 hour.

- Slowly add the talc to the coating dispersion and continue to stir for at least 2 hours.
- Screen the dispersion through a No. 60 mesh sieve.
- Continue to stir the screened coating dispersion throughout the coating process.

Coating Conditions for the Application of Opadry and AQOAT/Eudragit FS30D Aqueous Coating Dispersions

The following coating parameters were used for coating with the Opadry solution film coating.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	350 gram
Inlet Air Temperature	60 °C
Outlet Air Temperature	40 °C
Atomization Air Pressure	1.6 Bar

- Coat Levofloxacin pellets with Opadry coating solution such that you apply 3% coat weight gain to the pellets.

The following coating parameters were used for coating with the AQOATAS-HF/Eudragit FS30D film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	50 °C
Outlet Air Temperature	30 °C

Atomization Air Pressure 1.6 Bar

- Coat Opadry coated Levofloxacin pellets with the AQOATAS-HF/Eudragit FS30D coating dispersion such that you apply 30% coat weight gain to the pellets. Dry the coated pellets in the fluid bed for 20 minutes at 50°C.

Levofloxacin Colonic-Release Pellet Formulation and Preparation Procedure

Preparation of an Eudragit® S 100 Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit® S 100 dispersion applied to the Levofloxacin pellets is provided below in Table 5.

Table 5 Eudragit® S 100 Aqueous Coating Dispersion

Component	Percentage (%)
Part A	
Eudragit® S 100	12.0
1 N Ammonium Hydroxide	6.1
Triethyl Citrate	6.0
Purified Water	65.9
Part B	
Talc	2.0
Purified Water	8.0
Solid Content	20.0
Polymer Content	12.0

Preparation Procedure for an Eudragit® S 100 Aqueous Dispersion

Part A:

- Dispense Eudragit® S 100 powder in deionized water with stirring.

- Add ammonium hydroxide solution drop-wise into the dispersion with stirring.
- Allow the partially neutralized dispersion to stir for 60 minutes.
- Add triethyl citrate drop-wise into the dispersion with stirring. Stir for about 2 hours prior to the addition of Part B.

Part B:

- Disperse talc in the required amount of water
- Homogenize the dispersion using a PowerGen 700D high shear mixer.
- Part B is then added slowly to the polymer dispersion in Part A with a mild stirring.

Coating Conditions for the Application of Aqueous Coating Dispersions

The following coating parameters were used for coating of the Eudragit® S 100 aqueous film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	40 to 45 °C
Outlet Air Temperature	30 to 33 °C
Atomization Air Pressure	1.8 Bar
Pump Rate	2 gram per minute

- Coat pellets with S100 dispersion such that you apply 20% coat weight gain to the pellets.

Encapsulation of the Levofloxacin Pellets

Pellets are filled into hard gelatin capsules at a ratio of 25%: 25%: 25%: 25% Immediate-release pellets (uncoated), Eudragit L30 D-55 coated pellets 12% weight

gain, AQOAT AS-HF/Eudragit FS30D coated pellets 30% weight gain and Eudragit S100 coated pellets respectively.

The capsule is filled with the four different pellets to achieve a total dose of 250mg/capsule.

Tableting of the Levofloxacin Pellets

Levofloxacin Tablet Formula

Table 6 Levofloxacin Tablet

Component	Percentage (%)
Eudragit® S 100 coated pellets	12.0
Eudragit® L30D coated pellets	12.0
AQOAT/Eudragit® FS30D coated pellets	12.0
Emcocel 200	28.0
Levofloxacin	25.0
Povidone K90	2.5
Povidone K30	7.5
Magnesium stearate	1.0

Preparation Procedure for a Levofloxacin Tablet

- Blend all the components together except magnesium stearate for 10 minutes using a tumble blender.
- Add the magnesium stearate to the blend and blend for an additional 3 minutes.
- Compress the blend on a rotary tablet press to achieve a dose of 250 mg.

Four pulses

Example 62.

Metronidazole Pellet Formulation and Preparation Procedure

Pellet Formulation

The composition of the metronidazole pellets provided in Table 1.

Table 1 Composition of Metronidazole Pellets

Component	Percentage (%)
Metronidazole	93
Avicel PH 101	3
Methocel E5P LV	4
Purified Water	*
Total	100

*Removed during processing

Preparation Procedure for Metronidazole Pellets

- Blend metronidazole, Avicel® PH 101, and Methocel using a Robot Coupe high shear granulator.

- Add the purified water slowly into the powder blend under continuous mixing.

- Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator was 1.0 mm.

- Spheronize the extrudate using a Model SPH20 Caleva Spheronizer.

- Dry the spheronized pellets at 50°C until moisture level is < 3%.

- Pellets between 16 and 30 Mesh were collected for further processing.

Metronidazole Enteric-Release Pellet Formulation and Preparation Procedure

Preparation of an Eudragit® L 30 D-55 Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit L30D-55 coating dispersion applied to the metronidazole pellets is provided below in Table 2.

Table 2 Eudragit® L 30 D-55 Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30 D-55	55.0
Triethyl Citrate	1.6
Talc	8.0
Purified Water*	37.4
Solids Content	25.5
Polymer Content	15.9

*Removed during processing

Preparation Procedure for an Eudragit® L 30 D-55 Aqueous Dispersion

Suspend triethyl citrate and talc in deionized water.

The TEC/talc suspension is then homogenized using a PowerGen 700 high shear mixer.

Add the TEC/talc suspension slowly to the Eudragit® L 30 D-55 latex dispersion while stirring.

Allow the coating dispersion to stir for one hour prior to application onto the metronidazole pellets.

Coating Conditions for the Application of Eudragit L30D-55 Aqueous Coating Dispersion

The following coating parameters were used for coating of the Eudragit® L 30 D-55 film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	40 to 45 °C
Outlet Air Temperature	30 to 33 °C
Atomization Air Pressure	1.8 Bar
Pump Rate	2 gram per minute

- Coat metronidazole pellets with Eudragit L30 D-55 film coating dispersion such that you apply 12% coat weight gain to the pellets.

Metronidazole Delayed Enteric-Release Pellet Formulation and Preparation Procedure

Preparation of an Opadry Clear Coating Solution

Dispersion Formulation

The composition of the aqueous Opadry solution applied to the metronidazole pellets is provided below in Table 3.

Table 3 Opadry Clear Aqueous Coating Solution

Component	Percentage (%)
Opadry Clear YS-1-7006	7.0
Purified Water*	93.0
Solid Content %	7.0
Polymer Content %	7.0

*Removed during processing

Preparation Procedure for Opadry Clear Aqueous Solution

- Charge the purified water into a container
- Slowly add the Opadry Clear YS-1-7006 to the water with continuous mixing.

Preparation of an AQOAT AS-HF/Eudragit® FS30D Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous AQOAT AS-HF/ Eudragit FS30D coating dispersion applied to the Opadry coated metronidazole pellets is provided below in Table 4.

Table 4 AQOAT AS-HF/ Eudragit FS 30D Coating Dispersion

Component	Percentage (%)
AQOAT AS-HF	5.25
Eudagit FS30D	5.83
Triethyl Citrate	1.96
Sodium Lauryl Sulfate	0.21
Talc	2.10
Purified Water*	84.65
Solid Content	11.27
Polymer Content	7.0

*Removed during processing

Preparation Procedure for AQOAT AS-HF/ Eudragit FS30D Aqueous Dispersion

- Disperse triethyl citrate in purified water with stirring.
- Slowly add sodium lauryl sulfate into the triethyl citrate dispersion with stirring.
- Slowly add the AQOAT AS-HF powder to the dispersion above and stir for a minimum of 30 minutes.
- Slowly add the Eudragit FS30D dispersion to the AQOAT AS-HF dispersion and continue to stir for a minimum of 1 hour.

- Slowly add the talc to the coating dispersion and continue to stir for at least 2 hours.
- Screen the dispersion through a No. 60 mesh sieve.
- Continue to stir the screened coating dispersion throughout the coating process.

Coating Conditions for the Application of Opadry and AQOAT/Eudragit FS30D Aqueous Coating Dispersions

The following coating parameters were used for coating with the Opadry solution film coating.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	350 gram
Inlet Air Temperature	60 °C
Outlet Air Temperature	40 °C
Atomization Air Pressure	1.6 Bar

- Coat metronidazole pellets with Opadry coating solution such that you apply 3% coat weight gain to the pellets.

The following coating parameters were used for coating with the AQOATAS-HF/Eudragit FS30D film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	50 °C
Outlet Air Temperature	30 °C

Atomization Air Pressure 1.6 Bar

- Coat Opadry coated metronidazole pellets with the AQOATAS-HF/Eudragit FS30D coating dispersion such that you apply 30% coat weight gain to the pellets. Dry the coated pellets in the fluid bed for 20 minutes at 50°C.

Metronidazole Colonic-Release Pellet Formulation and Preparation Procedure

Preparation of an Eudragit® S 100 Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit® S 100 dispersion applied to the metronidazole pellets is provided below in Table 5.

Table 5 Eudragit® S 100 Aqueous Coating Dispersion

Component	Percentage (%)
Part A	
Eudragit® S 100	12.0
1 N Ammonium Hydroxide	6.1
Triethyl Citrate	6.0
Purified Water	65.9
Part B	
Talc	2.0
Purified Water	8.0
Solid Content	20.0
Polymer Content	12.0

Preparation Procedure for an Eudragit® S 100 Aqueous Dispersion

Part A:

- Dispense Eudragit® S 100 powder in deionized water with stirring.

- Add ammonium hydroxide solution drop-wise into the dispersion with stirring.
- Allow the partially neutralized dispersion to stir for 60 minutes.
- Add triethyl citrate drop-wise into the dispersion with stirring. Stir for about 2 hours prior to the addition of Part B.

Part B:

- Disperse talc in the required amount of water
- Homogenize the dispersion using a PowerGen 700D high shear mixer.
- Part B is then added slowly to the polymer dispersion in Part A with a mild stirring.

Coating Conditions for the Application of Aqueous Coating Dispersions

The following coating parameters were used for coating of the Eudragit® S 100 aqueous film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	40 to 45 °C
Outlet Air Temperature	30 to 33 °C
Atomization Air Pressure	1.8 Bar
Pump Rate	2 gram per minute

- Coat pellets with S100 dispersion such that you apply 20% coat weight gain to the pellets.

Encapsulation of the Metronidazole Pellets

Pellets are filled into size 00 hard gelatin capsules at a ratio of 20%: 30%: 20%: 30% Immediate-release pellets (uncoated), Eudragit L30 D-55 coated pellets 12% weight

gain, AQOAT AS-HF/Eudragit FS30D coated pellets 30% weight gain and Eudragit S100 coated pellets respectively.

The capsule is filled with the four different pellets to achieve a total dose of 375mg/capsule.

Tabletting of the Metronidazole Pellets

Metronidazole Tablet Formula

Table 6 Metronidazole Tablet

Component	Percentage (%)
Eudragit® S 100 coated pellets	12.0
Eudragit® L30D coated pellets	12.0
AQOAT/Eudragit® FS30D coated pellets	12.0
Emcocel 200	28.0
Metronidazole	25.0
Povidone K90	2.5
Povidone K30	7.5
Magnesium stearate	1.0

Preparation Procedure for a Metronidazole Tablet

- Blend all the components together except magnesium stearate for 10 minutes using a tumble blender.
- Add the magnesium stearate to the blend and blend for an additional 3 minutes.
- Compress the blend on a rotary tablet press to achieve a dose of 375 mg.

Four pulses

Example 62.

Doxycycline hyclate Pellet Formulation and Preparation Procedure

Pellet Formulation

The composition of the Doxycycline hyclate pellets provided in Table 1.

Table 1 Composition of Doxycycline hyclate Pellets

Component	Percentage (%)
Doxycycline hyclate	93
Avicel PH 101	3
Methocel E5P LV	4
Purified Water	*
Total	100

*Removed during processing

Preparation Procedure for Doxycycline hyclate Pellets

- Blend Doxycycline hyclate, Avicel® PH 101, and Methocel using a Robot Coupe high shear granulator.

- Add the purified water slowly into the powder blend under continuous mixing.
- Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator was 1.0 mm.
- Spheronize the extrudate using a Model SPH20 Caleva Spheronizer.
- Dry the spheronized pellets at 50°C until moisture level is < 3%.
- Pellets between 16 and 30 Mesh were collected for further processing.

Doxycycline hyclate Enteric-Release Pellet Formulation and Preparation Procedure

Preparation of an Eudragit® L 30 D-55/Eudragit NE 30D Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit L30D-55/Eudragit NE 30D aqueous coating dispersion applied to the doxycycline hyclate pellets is provided below in Table 2.

Table 2 Eudragit® L 30 D-55/Eudragit NE 30D Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30D-55	44.4
Eudragit NE 30D	14.8
Triethyl Citrate	1.3
Imwitor 900	0.9
Purified Water*	38.6
Solid Content	20.6
Polymer Content	16.4

*Removed during processing

Preparation Procedure for an Eudragit® L 30D-55/Eudragit NE 30D Aqueous Dispersion

- Heat purified water to 75-80°C and then add triethyl citrate (TEC) and Imwitor 900. Homogenize dispersion until temperature is less than 55°C.

- The TEC/Imwitor 900 dispersion is then stirred until the temperature is less than 35°C.
- Add the TEC/Imwitor 900 dispersion to Eudragit L30D-55 latex dispersion and stir for at least 30 minutes.
- Add Eudragit NE 30D to the Eudragit L30D/TEC/Imwitor 900 dispersion and stir for at least 10 minutes.
- Screen the dispersion through a No. 60 mesh sieve prior to coating.
- Continue to stir the dispersion until the coating process is complete.

Coating Conditions for the Application of Eudragit L30D-55/Eudragit NE 30DAqueous Coating Dispersion

The following coating parameters were used for coating of the Eudragit® L 30 D-55/Eudragit NE30D film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	45 °C
Outlet Air Temperature	32 to 35 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	3-4 gram per minute

Coat doxycycline hyclate pellets with Eudragit L30 D-55/Eudragit NE 30D film coating dispersion such that you apply 20% coat weight gain to the pellets.

Doxycycline hyclate Delayed Enteric-Release Pellet Formulation and Preparation Procedure

Preparation of an Opadry Clear Coating Solution

Dispersion Formulation

The composition of the aqueous Opadry solution applied to the Doxycycline hyclate pellets is provided below in Table 3.

Table 3 Opadry Clear Aqueous Coating Solution

Component	Percentage (%)
Opadry Clear YS-1-7006	7.0
Purified Water*	93.0
Solid Content %	7.0
Polymer Content %	7.0

*Removed during processing

Preparation Procedure for Opadry Clear Aqueous Solution

- Charge the purified water into a container
- Slowly add the Opadry Clear YS-1-7006 to the water with continuous mixing.

Preparation of an Eudragit® FS 30D/Eudragit L 30D-55 Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit FS 30D/Eudragit L 30D-55 coating dispersion applied to the Opadry coated Doxycycline hyclate pellets is provided below in Table 4.

Table 4 AQOAT AS-HF/ Eudragit FS 30D Coating Dispersion

Component	Percentage (%)
Eudragit L 30D-55	5.8
Eudagit FS 30D	17.5
Triethyl Citrate	1.3
Talc	1.4
Purified Water*	74.0
Solid Content	9.7
Polymer Content	7.0

*Removed during processing

Preparation Procedure for Eudragit FS 30D/Eudragit L 30D-55 Aqueous Dispersion

- Disperse triethyl citrate in purified water with stirring.
- Slowly add talc into the triethyl citrate dispersion with stirring.
- Slowly add the Eudragit L 30D-55 to the dispersion above and stir for a minimum of 10 minutes.
- Slowly add the Eudragit FS 30D dispersion to the Eudragit L 30D-55 dispersion and continue to stir for a minimum of 1 hour.
- Screen the dispersion through a No. 60 mesh sieve.

- Continue to stir the screened coating dispersion throughout the coating process.

Coating Conditions for the Application of Opadry and Eudragit FS 30D/ Eudragit L 30D-55 Aqueous Coating Dispersions

The following coating parameters were used for coating with the Opadry solution film coating.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	350 gram
Inlet Air Temperature	60 °C
Outlet Air Temperature	40 °C
Atomization Air Pressure	1.6 Bar

- Coat Doxycycline hyclate pellets with Opadry coating solution such that you apply 3% coat weight gain to the pellets.

The following coating parameters were used for coating with the Eudragit FS 30D/Eudragit L30D-55 film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	50 °C
Outlet Air Temperature	30 °C
Atomization Air Pressure	1.6 Bar

- Coat Opadry coated Doxycycline hyclate pellets with the Eudragit FS30D/ Eudragit L 30D-55 coating dispersion such that you apply 20% coat weight gain to the pellets.

Doxycycline hyclate Colonic-Release Pellet Formulation and Preparation Procedure

Preparation of an Eudragit® FS30D Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit® FS 30D dispersion applied to the doxycycline hyclate pellets is provided below in Table 4.

Table 4 Eudragit® FS 30D Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® FS 30D	54.8
Triethyl Citrate	0.9
Talc	3.3
Purified Water*	41.0
Solid Content	20.6
Polymer Content	16.4

*Removed during processing

Preparation Procedure for an Eudragit® FS 30D Aqueous Dispersion

- Disperse triethyl citrate (TEC) in the purified water.
- Add the talc in the triethyl citrate dispersion.
- Homogenize the dispersion using a homogenizer.
- Add slowly the Eudragit® FS 30D dispersion to the talc/TEC dispersion with stirring.
- Continue to stir the coating dispersion until the coating process is complete.

Coating Conditions for the Application of Eudragit FS30D Aqueous Coating Dispersion

The following coating parameters were used for coating with each of the Eudragit® FS 30 D aqueous film coating.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.2 mm
Material Charge	300 gram
Inlet Air Temperature	38 °C
Outlet Air Temperature	22 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	6 gram per minute

Coat pellets with Eudragit FS 30D coating dispersion dispersion such that you apply 30% coat weight gain to the pellets.

Encapsulation of the Doxycycline hyclate Pellets

Pellets are filled into hard gelatin capsules at a ratio of 25%: 25%: 25%: 25% Immediate-Release Pellets (uncoated), Eudragit L30 D-55/Eudragit NE 30D coated pellets 20% weight gain, Eudragit FS 30D/ Eudragit L 30 D-55 coated pellets 20% weight gain and Eudragit FS 30D coated pellets respectively.

The capsule is filled with the four different pellets to achieve a total dose of 100mg/capsule or 200mg/capsule.

Four Pulses

Example 62

Clarithromycin Pellet Formulation and Preparation Procedure

Pellet Formulation
The composition of the clarithromycin pellets provided in Table 1.

Table 1 Composition of Clarithromycin Pellets

Component	Percentage (%)
Clarithromycin	77.0
Lactose monohydrate, spray dried	11.0
Croscarmellose sodium	5.0
Polyoxyl 35 Castor Oil*	5.0
Hydroxypropyl methylcellulose*	2.0
Purified water	*
Total	100

*Removed during processing

Preparation Procedure for Clarithromycin Pellets

- Prepare the binder solution by adding the Polyoxyl to the purified water while stirring. After that is mixed, slowly add the hydroxypropyl methylcellulose and continue to stir until a solution is achieved.
- Blend clarithromycin, lactose monohydrate, and croscarmellose sodium using a Robot Coupe high shear granulator.

- Add binder solution slowly into the powder blend under continuous mixing.
- Granulate the powders in the high shear granulator with the binder solution.
- Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator was 1.0 mm.
- Spheronize the extrudate using a Model SPH20 Caleva Spheronizer.
- Dry the spheronized pellets at 50°C until the moisture level is > 3%.
- Pellets between 16 and 30 Mesh were collected for further processing.

Clarithromycin Enteric-Release Pellet Formulation and Preparation Procedure

Preparation of an Eudragit® L 30 D-55/Eudragit NE 30D Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit L30D-55/Eudragit NE 30D aqueous coating dispersion applied to the clarithromycin pellets is provided below in Table 2.

Table 2 Eudragit® L 30 D-55/Eudragit NE 30D Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30D-55	44.4
Eudragit NE 30D	14.8
Triethyl Citrate	1.3
Imwitor 900	0.9
Purified Water*	38.6
Solid Content	20.6
Polymer Content	16.4

*Removed during processing

Preparation Procedure for an Eudragit® L 30D-55/Eudragit NE 30D Aqueous Dispersion

- Heat purified water to 75-80°C and then add triethyl citrate (TEC) and Imwitor 900. Homogenize dispersion until temperature is less than 55°C.
- The TEC/Imwitor 900 dispersion is then stirred until the temperature is less than 35°C.

- Add the TEC/Imwitor 900 dispersion to Eudragit L30D-55 latex dispersion and stir for at least 30 minutes.
- Add Eudragit NE 30D to the Eudragit L30D/TEC/Imwitor 900 dispersion and stir for at least 10 minutes.
- Screen the dispersion through a No. 60 mesh sieve prior to coating.
- Continue to stir the dispersion until the coating process is complete.

Coating Conditions for the Application of Eudragit L30D-55/Eudragit NE 30DAqueous Coating Dispersion

The following coating parameters were used for coating of the Eudragit® L 30 D-55/Eudragit NE30D film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	45 °C
Outlet Air Temperature	32 to 35 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	3-4 gram per minute

Coat clarithromycin pellets with Eudragit L30 D-55/Eudragit NE 30D film coating dispersion such that you apply 20% coat weight gain to the pellets.

Clarithromycin Delayed Enteric-Release Pellets Formulation and Preparation Procedure

Preparation of an AQOAT AS-HF Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous AQOAT AS-HF aqueous coating dispersion applied to the clarithromycin pellets is provided below in Table 3.

Table 3 AQOAT AS-HF Aqueous Coating Dispersion

Component	Percentage (%)
AQOAT AS-HF	7.0
Triethyl Citrate	2.0
Talc	2.1
Sodium lauryl sulfate	0.2
Purified Water*	88.7
Solid Content	11.3
Polymer Content	7.0

*Removed during processing

Preparation Procedure for an AQOAT AS-HF Aqueous Dispersion

- Add triethyl citrate (TEC) to the purified water with stirring.
- Add the sodium lauryl sulfate (SLS) to the TEC dispersion with stirring and completely until completely dissolved.
- Add the AQOAT to the TEC/SLS dispersion and stir for at least 30 minutes.
- Add the talc to the AQOAT dispersion and until completely mixed and for at least 30 minutes.

- Screen the dispersion through a No. 60 mesh sieve prior to coating.
- Continue to stir the dispersion until the coating process is complete.

Coating Conditions for the Application of AQOAT AS-HF Aqueous Coating Dispersion

The following coating parameters were used for coating of the AQOAT AS-HF film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	48 °C
Outlet Air Temperature	27 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	3-4 gram per minute

Coat clarithromycin pellets with AQOAT AS-HF film coating dispersion such that you apply 30-35% coat weight gain to the pellets.

Clarithromycin Colonic-Release Pellets Formulation and Preparation Procedure

Preparation of an Eudragit® FS30D Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit® FS 30D dispersion applied to the clarithromycin pellets is provided below in Table 4.

Table 4 Eudragit® FS 30D Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® FS 30D	54.8
Triethyl Citrate	0.9
Talc	3.3
Purified Water*	41.0
Solid Content	20.6
Polymer Content	16.4

*Removed during processing

Preparation Procedure for an Eudragit® FS 30D Aqueous Dispersion

- Disperse triethyl citrate (TEC) in the purified water.
- Add the talc in the triethyl citrate dispersion.
- Homogenize the dispersion using a homogenizer.
- Add slowly the Eudragit® FS 30D dispersion to the talc/TEC dispersion with stirring.
- Continue to stir the coating dispersion until the coating process is complete.

Coating Conditions for the Application of Eudragit FS30D Aqueous Coating Dispersion

The following coating parameters were used for coating with each of the Eudragit® FS 30 D aqueous film coating.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.2 mm
Material Charge	300 gram
Inlet Air Temperature	38 °C
Outlet Air Temperature	22 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	6 gram per minute

Coat pellets with Eudragit FS 30D coating dispersion dispersion such that you apply 30% coat weight gain to the pellets.

Encapsulation of the Clarithromycin Pellets

Pellets are filled into hard gelatin capsules at a ratio of 25%: 25%: 25%: 25% Immediate-Release Pellets (uncoated),Eudragit L30 D-55/Eudagit NE 30D coated pellets 20% weight gain, AQOAT AS-HF coated pellets 30 -35% weight gain and Eudragit FS 30D coated pellets respectively.

The capsule is filled with the four different pellets to achieve a total dose of 250mg/capsule.

Tableting of the Clarithromycin Pellets

Clarithromycin Tablet Formula

Table 5 Clarithromycin Tablet

Component	Percentage (%)
Eudragit® L30D/NE 30D coated pellets	20.0
AQOAT AS-HF coated pellets	20.0
Eudargit FS 30D coated pellets	20.0
Emcocel	24.5
Clarithromycin	12.5
Povidone K30	2.0
Magnesium stearate	1.0
Purified water	*

*Removed during processing

Preparation Procedure for a Clarithromycin Tablet

- Blend all the components together except coated pellets and magnesium stearate for 10 minutes using a granulator.
- Granulate the blend with purified water.
- Screen the granulate through a No. 16 mesh sieve.
- Dry the screened granulate in a fluid bed dryer at 50-60°C until the moisture level is less than 3%.
- Add the dry granulate, coated pellets to a tumble blender and blend for 10 minutes.
- Add to the blend the magnesium stearate and blend an additional 3 minutes.
- Compress the blend on a rotary tablet press to achieve a dose of 500 mg.

Four pulses

Example 62.

Ciprofloxacin Pellet Formulation and Preparation Procedure

Pellet Formulation

The composition of the Ciprofloxacin pellets provided in Table 1.

Table 1 Composition of Ciprofloxacin Pellets

Component	Percentage (%)
Ciprofloxacin	93
Avicel PH 101	3

Methocel E5P LV	4
Purified Water	*
Total	100

*Removed during processing

Preparation Procedure for Ciprofloxacin Pellets

- Blend Ciprofloxacin, Avicel® PH 101, and Methocel using a Robot Coupe high shear granulator.
- Add the purified water slowly into the powder blend under continuous mixing.
- Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator was 1.0 mm.
- Spheronize the extrudate using a Model SPH20 Caleva Spheronizer.
- Dry the spheronized pellets at 50°C until moisture level is < 3%.
- Pellets between 16 and 30 Mesh were collected for further processing.

Ciprofloxacin Enteric-Release Pellet Formulation and Preparation Procedure

Preparation of an Eudragit® L 30 D-55/Eudragit NE 30D Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit L30D-55/Eudragit NE 30D aqueous coating dispersion applied to the Ciprofloxacin pellets is provided below in Table 2.

Table 2 Eudragit® L 30 D-55/Eudragit NE 30D Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30D-55	44.4
Eudragit NE 30D	14.8
Triethyl Citrate	1.3
Imwitor 900	0.9
Purified Water*	38.6
Solid Content	20.6
Polymer Content	16.4

*Removed during processing

Preparation Procedure for an Eudragit® L 30D-55/Eudragit NE 30D Aqueous Dispersion

- Heat purified water to 75-80°C and then add triethyl citrate (TEC) and Imwitor 900. Homogenize dispersion until temperature is less than 55°C.
- The TEC/Imwitor 900 dispersion is then stirred until the temperature is less than 35°C.

- Add the TEC/Imwitor 900 dispersion to Eudragit L30D-55 latex dispersion and stir for at least 30 minutes.
- Add Eudragit NE 30D to the Eudragit L30D/TEC/Imwitor 900 dispersion and stir for at least 10 minutes.
- Screen the dispersion through a No. 60 mesh sieve prior to coating.
- Continue to stir the dispersion until the coating process is complete.

Coating Conditions for the Application of Eudragit L30D-55/Eudragit NE 30DAqueous Coating Dispersion

The following coating parameters were used for coating of the Eudragit® L 30 D-55/Eudragit NE30D film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	45 °C
Outlet Air Temperature	32 to 35 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	3-4 gram per minute

Coat Ciprofloxacin pellets with Eudragit L30 D-55/Eudragit NE 30D film coating dispersion such that you apply 20% coat weight gain to the pellets.

Ciprofloxacin Delayed Enteric-Release Pellet Formulation and Preparation Procedure

Preparation of an Opadry Clear Coating Solution

Dispersion Formulation

The composition of the aqueous Opadry solution applied to the Ciprofloxacin pellets is provided below in Table 3.

Table 3 Opadry Clear Aqueous Coating Solution

Component	Percentage (%)
Opadry Clear YS-1-7006	7.0
Purified Water*	93.0
Solid Content %	7.0
Polymer Content %	7.0

*Removed during processing

Preparation Procedure for Opadry Clear Aqueous Solution

- Charge the purified water into a container
- Slowly add the Opadry Clear YS-1-7006 to the water with continuous mixing.

Preparation of an Eudragit® FS 30D/Eudragit L 30D-55 Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit FS 30D/Eudragit L 30D-55 coating dispersion applied to the Opadry coated Ciprofloxacin pellets is provided below in Table 4.

Table 4 Eudragit FS 30D/Eudragit L 30D-55 Coating Dispersion

Component	Percentage (%)
Eudragit L 30D-55	5.8
Eudagit FS 30D	17.5
Triethyl Citrate	1.3
Talc	1.4
Purified Water*	74.0
Solid Content	9.7
Polymer Content	7.0

*Removed during processing

Preparation Procedure for Eudragit FS 30D/Eudragit L 30D-55 Aqueous Dispersion

- Disperse triethyl citrate in purified water with stirring.
- Slowly add talc into the triethyl citrate dispersion with stirring.
- Slowly add the Eudragit L 30D-55 to the dispersion above and stir for a minimum of 10 minutes.
- Slowly add the Eudragit FS 30D dispersion to the Eudragit L 30D-55 dispersion and continue to stir for a minimum of 1 hour.
- Screen the dispersion through a No. 60 mesh sieve.

- Continue to stir the screened coating dispersion throughout the coating process.

Coating Conditions for the Application of Opadry and Eudragit FS 30D/ Eudragit L 30D-55 Aqueous Coating Dispersions

The following coating parameters were used for coating with the Opadry solution film coating.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	350 gram
Inlet Air Temperature	60 °C
Outlet Air Temperature	40 °C
Atomization Air Pressure	1.6 Bar

- Coat Ciprofloxacin pellets with Opadry coating solution such that you apply 3% coat weight gain to the pellets.

The following coating parameters were used for coating with the Eudragit FS 30D/Eudragit L30D-55 film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	50 °C
Outlet Air Temperature	30 °C
Atomization Air Pressure	1.6 Bar

- Coat Opadry coated Ciprofloxacin pellets with the Eudragit FS30D/ Eudragit L 30D-55 coating dispersion such that you apply 20% coat weight gain to the pellets.

Ciprofloxacin Colonic-Release Pellet Formulation and Preparation Procedure

Preparation of an Eudragit® FS 30D Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit® FS 30D dispersion applied to the Ciprofloxacin pellets is provided below in Table 4.

Table 4 Eudragit® FS 30D Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® FS 30D	54.8
Triethyl Citrate	0.9
Talc	3.3
Purified Water*	41.0
Solid Content	20.6
Polymer Content	16.4

*Removed during processing

Preparation Procedure for an Eudragit® FS 30D Aqueous Dispersion

- Disperse triethyl citrate (TEC) in the purified water.
- Add the talc in the triethyl citrate dispersion.
- Homogenize the dispersion using a homogenizer.
- Add slowly the Eudragit® FS 30D dispersion to the talc/TEC dispersion with stirring.
- Continue to stir the coating dispersion until the coating process is complete.

Coating Conditions for the Application of Eudragit FS30D Aqueous Coating Dispersion

The following coating parameters were used for coating with each of the Eudragit® FS 30 D aqueous film coating.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.2 mm
Material Charge	300 gram
Inlet Air Temperature	38 °C
Outlet Air Temperature	22 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	6 gram per minute

Coat pellets with Eudragit FS 30D coating dispersion dispersion such that you apply 30% coat weight gain to the pellets.

Encapsulation of the Ciprofloxacin Pellets

Pellets are filled into hard gelatin capsules at a ratio of 25%: 25%: 25%: 25% Immediate-Release Pellets (uncoated), Eudragit L30 D-55/Eudragit NE 30D coated pellets 20% weight gain, Eudragit FS 30D/ Eudragit L 30 D-55 coated pellets 20% weight gain and Eudragit FS 30D coated pellets respectively.

The capsule is filled with the four different pellets to achieve a total dose of 250mg/capsule.

Tableting of the Ciprofloxacin Pellets

Ciprofloxacin Tablet Formula

Table 6 Ciprofloxacin Tablet

Component	Percentage (%)
Eudragit® FS 30D coated pellets	12.0
Eudragit® L30D/NE coated pellets	12.0
Eudragit® FS 30D/L30D coated pellets	12.0
Emcocel 200	28.0
Ciprofloxacin	25.0
Povidone K90	2.5
Povidone K30	7.5
Magnesium stearate	1.0

Preparation Procedure for a Ciprofloxacin Tablet

- Blend all the components together except magnesium stearate for 10 minutes using a tumble blender.
- Add the magnesium stearate to the blend and blend for an additional 3 minutes.
- Compress the blend on a rotary tablet press to achieve a dose of 500 mg or 750 mg.

Four pulses

Example 62

Amoxicillin Pellet Formulation and Preparation Procedure

Pellet Formulations

The composition of the Amoxicillin trihydrate pellets provided in Table 1.

Table 1 Composition of Amoxicillin Pellets

Component	Percentage (%)
Amoxicillin Trihydrate powder	92
Avicel PH 101	6.0
Polyoxyl 35 Castor Oil*	1.0
Hydroxypropyl methylcellulose, NF*	1.0
Purified Water	**
Total	100

*Hydroxypropyl methylcellulose and Cremaphor EL were added as a 2.9% w/w aqueous solution during wet massing.

**Removed during processing

Preparation Procedure for Amoxicillin Pellets

- Blend Amoxicillin and Avicel® PH 101 using a low shear blender.
- Add the hydroxypropyl methylcellulose and Polyoxyl 35 Castor Oil binder solution slowly into the powder blend under continuous mixing.
- Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator is 0.8 mm.
- Spheronize the extrudate using a QJ-230 Spheronizer using a small cross section plate.
- Dry the spheronized pellets at 60°C using a fluid bed dryer until the exhaust temperature reaches 40°C.
- Pellets between 20 and 40 Mesh were collected for further processing.

Amoxicillin Enteric-Release Pellet Formulation and Preparation Procedure

Preparation of an Eudragit® L 30 D-55/Eudragit NE 30D Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit L30D-55/Eudragit NE 30D aqueous coating dispersion applied to the amoxicillin pellets is provided below in Table 2.

Table 2 Eudragit® L 30 D-55/Eudragit NE 30D Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30D-55	44.4
Eudragit NE 30D	14.8
Triethyl Citrate	1.3
Imwitor 900	0.9
Purified Water*	38.6
Solid Content	20.6
Polymer Content	16.4

*Removed during processing

Preparation Procedure for an Eudragit® L 30D-55/Eudragit NE 30D Aqueous Dispersion

- Heat purified water to 75-80°C and then add triethyl citrate (TEC) and Imwitor 900. Homogenize dispersion until temperature is less than 55°C.
- The TEC/Imwitor 900 dispersion is then stirred until the temperature is less than 35°C.
- Add the TEC/Imwitor 900 dispersion to Eudragit L30D-55 latex dispersion and stir for at least 30 minutes.

- Add Eudragit NE 30D to the Eudragit L30D/TEC/Imwitor 900 dispersion and stir for at least 10 minutes.
- Screen the dispersion through a No. 60 mesh sieve prior to coating.
- Continue to stir the dispersion until the coating process is complete.

Coating Conditions for the Application of Eudragit L30D-55/Eudragit NE 30DAqueous Coating Dispersion

The following coating parameters were used for coating of the Eudragit® L 30 D-55/Eudragit NE30D film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	45 °C
Outlet Air Temperature	32 to 35 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	3-4 gram per minute

Coat Amoxicillin pellets with Eudragit L30 D-55/Eudragit NE 30D film coating dispersion such that you apply 20% coat weight gain to the pellets.

Amoxicillin Delayed Enteric-Release Pellets Formulation and Preparation Procedure

Preparation of an AQOAT AS-HF Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous AQOAT AS-HF aqueous coating dispersion applied to the amoxicillin pellets is provided below in Table 3.

Table 3 AQOAT AS-HF Aqueous Coating Dispersion

Component	Percentage (%)
AQOAT AS-HF	7.0
Triethyl Citrate	2.0
Talc	2.1
Sodium lauryl sulfate	0.2
Purified Water*	88.7
Solid Content	11.3
Polymer Content	7.0

*Removed during processing

Preparation Procedure for an AQOAT AS-HF Aqueous Dispersion

- Add triethyl citrate (TEC) to the purified water with stirring.
- Add the sodium lauryl sulfate (SLS) to the TEC dispersion with stirring and completely until completely dissolved.
- Add the AQOAT to the TEC/SLS dispersion and stir for at least 30 minutes.
- Add the talc to the AQOAT dispersion and until completely mixed and for at least 30 minutes.
- Screen the dispersion through a No. 60 mesh sieve prior to coating.
- Continue to stir the dispersion until the coating process is complete.

Coating Conditions for the Application of AQOAT AS-HF Aqueous Coating Dispersion

The following coating parameters were used for coating of the AQOAT AS-HF film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	48 °C
Outlet Air Temperature	27 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	3-4 gram per minute

Coat amoxicillin pellets with AQOAT AS-HF film coating dispersion such that you apply 30-35% coat weight gain to the pellets.

Amoxicillin Colonic-Release Pellet Formulation and Preparation Procedure

Preparation of an Eudragit® FS 30D Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit® FS 30D dispersion applied to the Amoxicillin pellets is provided below in Table 4.

Table 4 Eudragit® FS 30D Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® FS 30D	54.8
Triethyl Citrate	0.9
Talc	3.3
Purified Water*	41.0
Solid Content	20.6
Polymer Content	16.4

*Removed during processing

Preparation Procedure for an Eudragit® FS 30D Aqueous Dispersion

- Disperse triethyl citrate (TEC) in the purified water.
- Add the talc in the triethyl citrate dispersion.
- Homogenize the dispersion using a homogenizer.
- Add slowly the Eudragit® FS 30D dispersion to the talc/TEC dispersion with stirring.

Continue to stir the coating dispersion until the coating process is complete.

Coating Conditions for the Application of Eudragit FS30D Aqueous Coating Dispersion

The following coating parameters were used for coating with each of the Eudragit® FS 30 D aqueous film coating.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed
Coater	
Spray nozzle diameter	1.2 mm
Material Charge	300 gram
Inlet Air Temperature	38 °C
Outlet Air Temperature	22 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	6 gram per minute

Coat pellets with Eudragit FS 30D coating dispersion dispersion such that you apply 30% coat weight gain to the pellets.

Amoxicillin Tablets

Preparation of Amoxicillin Granulation for tableting

Table 5 Composition of Amoxicillin Granulation (Immediate Release)

Component	Percentage (%)
Amoxicillin Trihydrate powder	92
Avicel PH 101	7.0
Hydroxypropyl methylcellulose, NF*	1.0
Total	100

*Hydroxypropyl methylcellulose was added as a

2.9% w/w aqueous solution during wet massing.

- Blend Amoxicillin and Avicel® PH 101 using a low shear blender.
- Add the hydroxypropyl methylcellulose binder solution slowly into the powder blend under continuous mixing.
- Dry the granulation at 60°C using a fluid bed dryer until the exhaust temperature reaches 40°C.
- Granules between 20 and 40 Mesh are collected for further processing.

Tableting of the Amoxicillin Pellets

Table 6 Composition of Amoxicillin Tablets

Component	Percentage (%)
Amoxicillin granules	32.5
Avicel PH 200	5.0
Eudragit L30D-55/NE 30D coated pellets	20
AQOAT coated pellets	20
Eudragit FS 30D coated pellets	20
Colloidal silicon dioxide	1.5
Magnesium stearate	1.0
Total	100

- Blend the Amoxicillin granules, Avicel PH-200, Amoxicillin coated pellets and colloidal silicon dioxide for 15 minutes in a tumble blender.
- Add the magnesium stearate to the blender, and blend for 5 minutes.
- Compress the blend on a rotary tablet press.
- The fill weight should be adjusted to achieve a 500 mg dose tablet.

Encapsulation of the Amoxicillin Pellets

Pellets are filled into hard gelatin capsules at a ratio of 30%: 30%: 20%: 20% Immediate-release pellets (uncoated), L30 D-55/Eudragit NE 30D coated pellets 20% weight gain, AQOAT coated pellets 30% weight gain and Eudragit FS 30D coated pellets respectively. The capsule is filled with the four different pellets to achieve a total dose of 250mg/capsule.

The present invention is particularly advantageous in that there is provided an antibiotic product which provides an improvement over twice a day administration of the antibiotic and an improvement over a once a day administration of the antibiotic.

Numerous modification and variations of the present invention are possible in light of the above teachings and therefore, within the scope of the appended claims the invention may be practiced otherwise than as particularly described.

Four Pulses

Example 63

Cefuroxime axetil Pellet Formulation and Preparation Procedure

Pellet Formulation

The composition of the Cefuroxime axetil pellets provided in Table 1.

Table 1 Composition of Cefuroxime axetil Pellets

Component	Percentage (%)
Cefuroxime axetil	77.0
Lactose monohydrate, spray dried	11.0
Croscarmellose sodium	5.0
Polyoxyl 35 Castor Oil*	5.0
Hydroxypropyl methylcellulose*	2.0
Purified water	*
Total	100

*Removed during processing

Preparation Procedure for Cefuroxime axetil Pellets

- Prepare the binder solution by adding the Polyoxyl to the purified water while stirring. After that is mixed, slowly add the hydroxypropyl methylcellulose and continue to stir until a solution is achieved.
- Blend Cefuroxime axetil, lactose monohydrate, and croscarmellose sodium using a Robot Coupe high shear granulator.
- Add binder solution slowly into the powder blend under continuous mixing.
- Granulate the powders in the high shear granulator with the binder solution.
- Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator was 1.0 mm.
- Spheronize the extrudate using a Model SPH20 Caleva Spheronizer.
- Dry the spheronized pellets at 50°C until the moisture level is > 3%.
- Pellets between 16 and 30 Mesh were collected for further processing.

Cefuroxime axetil Enteric-Release Pellet Formulation and Preparation

Procedure

Preparation of an Eudragit® L 30 D-55/Eudragit NE 30D Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit L30D-55/Eudragit NE 30D aqueous coating dispersion applied to the Cefuroxime axetil pellets is provided below in Table 2.

Table 2 Eudragit® L 30 D-55/Eudragit NE 30D Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30D-55	44.4
Eudragit NE 30D	14.8
Triethyl Citrate	1.3
Imwitor 900	0.9
Purified Water*	38.6
Solid Content	20.6
Polymer Content	16.4

*Removed during processing

Preparation Procedure for an Eudragit® L 30D-55/Eudragit NE 30D Aqueous Dispersion

- Heat purified water to 75-80°C and then add triethyl citrate (TEC) and Imwitor 900. Homogenize dispersion until temperature is less than 55°C.
- The TEC/Imwitor 900 dispersion is then stirred until the temperature is less than 35°C.

- Add the TEC/Imwitor 900 dispersion to Eudragit L30D-55 latex dispersion and stir for at least 30 minutes.
- Add Eudragit NE 30D to the Eudragit L30D/TEC/Imwitor 900 dispersion and stir for at least 10 minutes.
- Screen the dispersion through a No. 60 mesh sieve prior to coating.
- Continue to stir the dispersion until the coating process is complete.

Coating Conditions for the Application of Eudragit L30D-55/Eudragit NE 30DAqueous Coating Dispersion

The following coating parameters were used for coating of the Eudragit® L 30 D-55/Eudragit NE30D film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	45 °C
Outlet Air Temperature	32 to 35 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	3-4 gram per minute

Coat Cefuroxime axetil pellets with Eudragit L30 D-55/Eudragit NE 30D film coating dispersion such that you apply 20% coat weight gain to the pellets.

Cefuroxime axetil Delayed Enteric-Release Pellets Formulation and Preparation Procedure

Preparation of an AQOAT AS-HF Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous AQOAT AS-HF aqueous coating dispersion applied to the Cefuroxime axetil pellets is provided below in Table 3.

Table 3 AQOAT AS-HF Aqueous Coating Dispersion

Component	Percentage (%)
AQOAT AS-HF	7.0
Triethyl Citrate	2.0
Talc	2.1
Sodium lauryl sulfate	0.2
Purified Water*	88.7
Solid Content	11.3
Polymer Content	7.0

*Removed during processing

Preparation Procedure for an AQOAT AS-HF Aqueous Dispersion

- Add triethyl citrate (TEC) to the purified water with stirring.
- Add the sodium lauryl sulfate (SLS) to the TEC dispersion with stirring and completely until completely dissolved.
- Add the AQOAT to the TEC/SLS dispersion and stir for at least 30 minutes.
- Add the talc to the AQOAT dispersion and until completely mixed and for at least 30 minutes.

- Screen the dispersion through a No. 60 mesh sieve prior to coating.
- Continue to stir the dispersion until the coating process is complete.

Coating Conditions for the Application of AQOAT AS-HF Aqueous Coating Dispersion

The following coating parameters were used for coating of the AQOAT AS-HF film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	48 °C
Outlet Air Temperature	27 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	3-4 gram per minute

Coat Cefuroxime axetil pellets with AQOAT AS-HF film coating dispersion such that you apply 30-35% coat weight gain to the pellets.

Cefuroxime axetil Colonic-Release Pellets Formulation and Preparation Procedure

Preparation of an Eudragit® FS30D Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit® FS 30D dispersion applied to the Cefuroxime axetil pellets is provided below in Table 4.

Table 4 Eudragit® FS 30D Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® FS 30D	54.8
Triethyl Citrate	0.9
Talc	3.3
Purified Water*	41.0
Solid Content	20.6
Polymer Content	16.4

*Removed during processing

Preparation Procedure for an Eudragit® FS 30D Aqueous Dispersion

- Disperse triethyl citrate (TEC) in the purified water.
- Add the talc in the triethyl citrate dispersion.
- Homogenize the dispersion using a homogenizer.
- Add slowly the Eudragit® FS 30D dispersion to the talc/TEC dispersion with stirring.
- Continue to stir the coating dispersion until the coating process is complete.

Coating Conditions for the Application of Eudragit FS30D Aqueous Coating Dispersion

The following coating parameters were used for coating with each of the Eudragit® FS 30 D aqueous film coating.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.2 mm
Material Charge	300 gram
Inlet Air Temperature	38 °C
Outlet Air Temperature	22 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	6 gram per minute

Coat pellets with Eudragit FS 30D coating dispersion dispersion such that you apply 30% coat weight gain to the pellets.

Encapsulation of the Cefuroxime axetil Pellets

Pellets are filled into hard gelatin capsules at a ratio of 25%: 25%: 25%: 25% Immediate-Release Pellets (uncoated), Eudragit L30 D-55/Eudagit NE 30D coated pellets 20% weight gain, AQOAT AS-HF coated pellets 30 -35% weight gain and Eudragit FS 30D coated pellets respectively.

The capsule is filled with the four different pellets to achieve a total dose of 250mg/capsule.

Tableting of the Cefuroxime axetil Pellets

Cefuroxime axetil Tablet Formula

Table 5 Cefuroxime axetil Tablet

Component	Percentage (%)
Eudragit® L30D/NE 30D coated pellets	20.0
AQOAT AS-HF coated pellets	20.0
Eudargit FS 30D coated pellets	20.0
Emcocel	24.5
Cefuroxime axetil	12.5
Povidone K30	2.0
Magnesium stearate	1.0
Purified water	*

*Removed during processing

Preparation Procedure for a Cefuroxime axetil Tablet

- Blend all the components together except coated pellets and magnesium stearate for 10 minutes using a granulator.
- Granulate the blend with purified water.
- Screen the granulate through a No. 16 mesh sieve.
- Dry the screened granulate in a fluid bed dryer at 50-60°C until the moisture level is less than 3%.
- Add the dry granulate, coated pellets to a tumble blender and blend for 10 minutes.
- Add to the blend the magnesium stearate and blend an additional 3 minutes.
- Compress the blend on a rotary tablet press to achieve a dose of 500 mg.

The present invention is particularly advantageous in that there is provided an antibiotic product which provides an improvement over twice a day administration of the antibiotic and an improvement over a once a day administration of the antibiotic.

Numerous modification and variations of the present invention are possible in light of the above teachings and therefore, within the scope of the appended claims the invention may be practiced otherwise than as particularly described.

Four Pulses

Example 64

Cefodoxime proxetil Pellet Formulation and Preparation Procedure

Pellet Formulation

The composition of the Cefodoxime proxetil pellets provided in Table 1.

Table 1 Composition of Cefodoxime proxetil Pellets

Component	Percentage (%)
Cefodoxime proxetil	77.0
Lactose monohydrate, spray dried	11.0
Croscarmellose sodium	5.0
Polyoxyl 35 Castor Oil*	5.0
Hydroxypropyl methylcellulose*	2.0
Purified water	*
Total	100

*Removed during processing

Preparation Procedure for Cefodoxime proxetil Pellets

- Prepare the binder solution by adding the Polyoxyl to the purified water while stirring. After that is mixed, slowly add the hydroxypropyl methylcellulose and continue to stir until a solution is achieved.
- Blend Cefodoxime proxetil, lactose monohydrate, and croscarmellose sodium using a Robot Coupe high shear granulator.
- Add binder solution slowly into the powder blend under continuous mixing.
- Granulate the powders in the high shear granulator with the binder solution.

- Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator was 1.0 mm.
- Spheronize the extrudate using a Model SPH20 Caleva Spheronizer.
- Dry the spheronized pellets at 50°C until the moisture level is > 3%.
- Pellets between 16 and 30 Mesh were collected for further processing.

Cefodoxime proxetil Enteric-Release Pellet Formulation and Preparation

Procedure

Preparation of an Eudragit® L 30 D-55/Eudragit NE 30D Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit L30D-55/Eudragit NE 30D aqueous coating dispersion applied to the Cefodoxime proxetil pellets is provided below in Table 2.

Table 2 Eudragit® L 30 D-55/Eudragit NE 30D Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30D-55	44.4
Eudragit NE 30D	14.8
Triethyl Citrate	1.3
Imwitor 900	0.9
Purified Water*	38.6
Solid Content	20.6
Polymer Content	16.4

*Removed during processing

Preparation Procedure for an Eudragit® L 30D-55/Eudragit NE 30D Aqueous Dispersion

- Heat purified water to 75-80°C and then add triethyl citrate (TEC) and Imwitor 900. Homogenize dispersion until temperature is less than 55°C.
- The TEC/Imwitor 900 dispersion is then stirred until the temperature is less than 35°C.

- Add the TEC/Imwitor 900 dispersion to Eudragit L30D-55 latex dispersion and stir for at least 30 minutes.
- Add Eudragit NE 30D to the Eudragit L30D/TEC/Imwitor 900 dispersion and stir for at least 10 minutes.
- Screen the dispersion through a No. 60 mesh sieve prior to coating.
- Continue to stir the dispersion until the coating process is complete.

Coating Conditions for the Application of Eudragit L30D-55/Eudragit NE 30DAqueous Coating Dispersion

The following coating parameters were used for coating of the Eudragit® L 30 D-55/Eudragit NE30D film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	45 °C
Outlet Air Temperature	32 to 35 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	3-4 gram per minute

Coat Cefodoxime proxetil pellets with Eudragit L30 D-55/Eudragit NE 30D film coating dispersion such that you apply 20% coat weight gain to the pellets.

Cefodoxime proxetil Delayed Enteric-Release Pellets Formulation and Preparation Procedure

Preparation of an AQOAT AS-HF Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous AQOAT AS-HF aqueous coating dispersion applied to the Cefodoxime proxetil pellets is provided below in Table 3.

Table 3 AQOAT AS-HF Aqueous Coating Dispersion

Component	Percentage (%)
AQOAT AS-HF	7.0
Triethyl Citrate	2.0
Talc	2.1
Sodium lauryl sulfate	0.2
Purified Water*	88.7
Solid Content	11.3
Polymer Content	7.0

*Removed during processing

Preparation Procedure for an AQOAT AS-HF Aqueous Dispersion

- Add triethyl citrate (TEC) to the purified water with stirring.
- Add the sodium lauryl sulfate (SLS) to the TEC dispersion with stirring and completely until completely dissolved.
- Add the AQOAT to the TEC/SLS dispersion and stir for at least 30 minutes.
- Add the talc to the AQOAT dispersion and until completely mixed and for at least 30 minutes.

- Screen the dispersion through a No. 60 mesh sieve prior to coating.
- Continue to stir the dispersion until the coating process is complete.

Coating Conditions for the Application of AQOAT AS-HF Aqueous Coating Dispersion

The following coating parameters were used for coating of the AQOAT AS-HF film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	48 °C
Outlet Air Temperature	27 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	3-4 gram per minute

Coat Cefodoxime proxetil pellets with AQOAT AS-HF film coating dispersion such that you apply 30-35% coat weight gain to the pellets.

Cefodoxime proxetil Colonic-Release Pellets Formulation and Preparation Procedure

Preparation of an Eudragit® FS30D Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit® FS 30D dispersion applied to the Cefodoxime proxetil pellets is provided below in Table 4.

Table 4 Eudragit® FS 30D Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® FS 30D	54.8
Triethyl Citrate	0.9
Talc	3.3
Purified Water*	41.0
Solid Content	20.6
Polymer Content	16.4

*Removed during processing

Preparation Procedure for an Eudragit® FS 30D Aqueous Dispersion

- Disperse triethyl citrate (TEC) in the purified water.
- Add the talc in the triethyl citrate dispersion.
- Homogenize the dispersion using a homogenizer.
- Add slowly the Eudragit® FS 30D dispersion to the talc/TEC dispersion with stirring.
- Continue to stir the coating dispersion until the coating process is complete.

Coating Conditions for the Application of Eudragit FS30D Aqueous Coating Dispersion

The following coating parameters were used for coating with each of the Eudragit® FS 30 D aqueous film coating.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.2 mm
Material Charge	300 gram
Inlet Air Temperature	38 °C
Outlet Air Temperature	22 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	6 gram per minute

Coat pellets with Eudragit FS 30D coating dispersion dispersion such that you apply 30% coat weight gain to the pellets.

Encapsulation of the Cefodoxime proxetil Pellets

Pellets are filled into hard gelatin capsules at a ratio of 25%: 25%: 25%: 25% Immediate-Release Pellets (uncoated), Eudragit L30 D-55/Eudagit NE 30D coated pellets 20% weight gain, AQOAT AS-HF coated pellets 30 -35% weight gain and Eudragit FS 30D coated pellets respectively.

The capsule is filled with the four different pellets to achieve a total dose of 200mg/capsule.

Tableting of the Cefodoxime proxetil Pellets

Cefodoxime proxetil Tablet Formula

Table 5 Cefodoxime proxetil Tablet

Component	Percentage (%)
Eudragit® L30D/NE 30D coated pellets	20.0
AQOAT AS-HF coated pellets	20.0
Eudragit FS 30D coated pellets	20.0
Emcocel	24.5
Cefodoxime proxetil	12.5
Povidone K30	2.0
Magnesium stearate	1.0
Purified water	*

*Removed during processing

Preparation Procedure for a Cefodoxime proxetil Tablet

- Blend all the components together except coated pellets and magnesium stearate for 10 minutes using a granulator.
- Granulate the blend with purified water.
- Screen the granulate through a No. 16 mesh sieve.
- Dry the screened granulate in a fluid bed dryer at 50-60°C until the moisture level is less than 3%.
- Add the dry granulate, coated pellets to a tumble blender and blend for 10 minutes.
- Add to the blend the magnesium stearate and blend an additional 3 minutes.
- Compress the blend on a rotary tablet press to achieve a dose of 400 mg.

The present invention is particularly advantageous in that there is provided an antibiotic product which provides an improvement over twice a day administration of the antibiotic and an improvement over a once a day administration of the antibiotic.

Numerous modification and variations of the present invention are possible in light of the above teachings and therefore, within the scope of the appended claims the invention may be practiced otherwise than as particularly described.

Four pulses

Example 65

Dicloxacillin Pellet Formulation and Preparation Procedure

Pellet Formulations

The composition of the Dicloxacillin trihydrate pellets provided in Table 1.

Table 1 Composition of Dicloxacillin Pellets

Component	Percentage (%)
Dicloxacillin	92
Avicel PH 101	6.0
Polyoxyl 35 Castor Oil*	1.0
Hydroxypropyl methylcellulose, NF*	1.0
Purified Water	**
Total	100

*Hydroxypropyl methylcellulose and Polyoxyl 35 Castor Oil were added as a 2.9% w/w aqueous solution during wet massing.

**Removed during processing

Preparation Procedure for Dicloxacillin Pellets

- Blend Dicloxacillin and Avicel® PH 101 using a low shear blender.
- Add the hydroxypropyl methylcellulose and Polyoxyl 35 Castor Oil binder solution slowly into the powder blend under continuous mixing.
- Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator is 0.8 mm.
- Spheronize the extrudate using a QJ-230 Spheronizer using a small cross section plate.
- Dry the spheronized pellets at 60°C using a fluid bed dryer until the exhaust temperature reaches 40°C.
- Pellets between 20 and 40 Mesh were collected for further processing.

Dicloxacillin Enteric-Release Pellet Formulation and Preparation Procedure

Preparation of an Eudragit® L 30 D-55/Eudragit NE 30D Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit L30D-55/Eudragit NE 30D aqueous coating dispersion applied to the Dicloxacillin pellets is provided below in Table 2.

Table 2 Eudragit® L 30 D-55/Eudragit NE 30D Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30D-55	44.4
Eudragit NE 30D	14.8
Triethyl Citrate	1.3
Imwitor 900	0.9
Purified Water*	38.6
Solid Content	20.6
Polymer Content	16.4

*Removed during processing

Preparation Procedure for an Eudragit® L 30D-55/Eudragit NE 30D Aqueous Dispersion

- Heat purified water to 75-80°C and then add triethyl citrate (TEC) and Imwitor 900. Homogenize dispersion until temperature is less than 55°C.
- The TEC/Imwitor 900 dispersion is then stirred until the temperature is less than 35°C.
- Add the TEC/Imwitor 900 dispersion to Eudragit L30D-55 latex dispersion and stir for at least 30 minutes.

- Add Eudragit NE 30D to the Eudragit L30D/TEC/Imwitor 900 dispersion and stir for at least 10 minutes.
- Screen the dispersion through a No. 60 mesh sieve prior to coating.
- Continue to stir the dispersion until the coating process is complete.

Coating Conditions for the Application of Eudragit L30D-55/Eudragit NE 30DAqueous Coating Dispersion

The following coating parameters were used for coating of the Eudragit® L 30 D-55/Eudragit NE30D film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	45 °C
Outlet Air Temperature	32 to 35 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	3-4 gram per minute

Coat Dicloxacillin pellets with Eudragit L30 D-55/Eudragit NE 30D film coating dispersion such that you apply 20% coat weight gain to the pellets.

Dicloxacillin Delayed Enteric-Release Pellets Formulation and Preparation Procedure

Preparation of an AQOAT AS-HF Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous AQOAT AS-HF aqueous coating dispersion applied to the Dicloxacillin pellets is provided below in Table 3.

Table 3 AQOAT AS-HF Aqueous Coating Dispersion

Component	Percentage (%)
AQOAT AS-HF	7.0
Triethyl Citrate	2.0
Talc	2.1
Sodium lauryl sulfate	0.2
Purified Water*	88.7
Solid Content	11.3
Polymer Content	7.0

*Removed during processing

Preparation Procedure for an AQOAT AS-HF Aqueous Dispersion

- Add triethyl citrate (TEC) to the purified water with stirring.
- Add the sodium lauryl sulfate (SLS) to the TEC dispersion with stirring and completely until completely dissolved.
- Add the AQOAT to the TEC/SLS dispersion and stir for at least 30 minutes.
- Add the talc to the AQOAT dispersion and until completely mixed and for at least 30 minutes.
- Screen the dispersion through a No. 60 mesh sieve prior to coating.
- Continue to stir the dispersion until the coating process is complete.

Coating Conditions for the Application of AQOAT AS-HF Aqueous Coating Dispersion

The following coating parameters were used for coating of the AQOAT AS-HF film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	48 °C
Outlet Air Temperature	27 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	3-4 gram per minute

Coat Dicloxacillin pellets with AQOAT AS-HF film coating dispersion such that you apply 30-35% coat weight gain to the pellets.

Dicloxacillin Colonic-Release Pellet Formulation and Preparation Procedure

Preparation of an Eudragit® FS 30D Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit® FS 30D dispersion applied to the Dicloxacillin pellets is provided below in Table 4.

Table 4 Eudragit® FS 30D Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® FS 30D	54.8
Triethyl Citrate	0.9
Talc	3.3
Purified Water*	41.0
Solid Content	20.6
Polymer Content	16.4

*Removed during processing

Preparation Procedure for an Eudragit® FS 30D Aqueous Dispersion

- Disperse triethyl citrate (TEC) in the purified water.
- Add the talc in the triethyl citrate dispersion.
- Homogenize the dispersion using a homogenizer.
- Add slowly the Eudragit® FS 30D dispersion to the talc/TEC dispersion with stirring.

Continue to stir the coating dispersion until the coating process is complete.

Coating Conditions for the Application of Eudragit FS30D Aqueous Coating Dispersion

The following coating parameters were used for coating with each of the Eudragit® FS 30 D aqueous film coating.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed
Coater	
Spray nozzle diameter	1.2 mm
Material Charge	300 gram
Inlet Air Temperature	38 °C
Outlet Air Temperature	22 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	6 gram per minute

Coat pellets with Eudragit FS 30D coating dispersion dispersion such that you apply 30% coat weight gain to the pellets.

Encapsulation of the Dicloxacillin Pellets

Pellets are filled into hard gelatin capsules at a ratio of 25%: 25%: 25%: 25% Immediate-release pellets (uncoated), L30 D-55/Eudragit NE 30D coated pellets 20% weight gain, AQOAT coated pellets 30% weight gain and Eudragit FS 30D coated pellets respectively. The capsule is filled with the four different pellets to achieve a total dose of 250mg/capsule.

Dicloxacillin Tablets

Preparation of Dicloxacillin Granulation for tableting

Table 5 Composition of Dicloxacillin Granulation (Immediate Release)

Component	Percentage (%)
Dicloxacillin	92
Avicel PH 101	7.0
Hydroxypropyl methylcellulose, NF*	1.0
Total	100

*Hydroxypropyl methylcellulose was added as a 2.9% w/w aqueous solution during wet massing.

- Blend Dicloxacillin and Avicel® PH 101 using a low shear blender.
- Add the hydroxypropyl methylcellulose binder solution slowly into the powder blend under continuous mixing.
- Dry the granulation at 60°C using a fluid bed dryer until the exhaust temperature reaches 40°C.
- Granules between 20 and 40 Mesh are collected for further processing.

Tableting of the Dicloxacillin Pellets

Table 6 Composition of Dicloxacillin Tablets

Component	Percentage (%)
Dicloxacillin granules	32.5
Avicel PH 200	5.0
Eudragit L30D-55/NE 30D coated pellets	20
AQOAT coated pellets	20
Eudragit FS 30D coated pellets	20
Colloidal silicon dioxide	1.5
Magnesium stearate	1.0
Total	100

- Blend the Dicloxacillin granules, Avicel PH-200, Dicloxacillin coated pellets and colloidal silicon dioxide for 15 minutes in a tumble blender.
- Add the magnesium stearate to the blender, and blend for 5 minutes.
- Compress the blend on a rotary tablet press.

The fill weight should be adjusted to achieve a 500 mg dose tablet.

The present invention is particularly advantageous in that there is provided an antibiotic product which provides an improvement over twice a day administration of the antibiotic and an improvement over a once a day administration of the antibiotic.

Numerous modification and variations of the present invention are possible in light of the above teachings and therefore, within the scope of the appended claims the invention may be practiced otherwise than as particularly described.

WHAT IS CLAIMED IS:

1. An antibiotic product comprising: a first antibiotic dosage form, a second antibiotic dosage form, and a third antibiotic dosage form, each of said first, second and third antibiotic dosage forms comprising an antibiotic and a pharmaceutically acceptable carrier, said three dosage forms having different release profiles, said antibiotic product reaching a C_{max} in less than about twelve hours, wherein the antibiotic is selected from the group consisting of: levofloxacin, metronidazole, tetracycline, doxycycline, erythromyacin, clarithromycin, fluroquinilone, ciprofloxacin, betalactam antibiotic, cephalsporin, cefuroxime, cefpodoxime, penicillin, amoxicillin, and dicloxacillin; said first dosage form being an immediate release dosage form, said second and third dosage forms, each being a delayed release dosage form, wherein the antibiotic released from the first dosage form reaches a C_{max} in serum in from 0.5 to 2 hours after administration of the product, wherein the antibiotic released from the second dosage form reaches a C_{max} in serum in no more than 4 hours after administration of the product and after C_{max} is reached for antibiotic from the first dosage form and the antibiotic released from the third dosage form reaches a C_{max} in serum within 8 hours, and after the C_{max} is reached for the antibiotic released from the second dosage form.

2. The product of claim 1 wherein the second dosage form initiates release of the antibiotic at least one hour after the first dosage form.

3. The product of claim 2 wherein the C_{max} for the second dosage form is reached no earlier than two hours after product administration.

4. The product of claim 3 wherein the first dosage form contains from about 20% to about 50%, by weight, of the total antibiotic of the product, wherein the second dosage form contains from 30% to 60%, by weight, of the antibiotic that is contained in the second and third dosage forms.

5. The product of claim 4 wherein the first dosage form contains from 15% to 30%, by weight, of the total antibiotic present in the product.

6. The product of claim 1 wherein the product includes a fourth delayed release antibiotic dosage form having a different release profile from the first, second and third dosage forms.

7. The product of claim 6 wherein the second dosage form contains from 20% to 35%, by weight, of the total antibiotic present in the second, third and fourth dosage forms, the third dosage form contains from 20% to 40%, by weight, of the

total antibiotic present in the second, third and fourth dosage forms, with the remainder being present in the fourth dosage form.

8. The product of claim 1 wherein C_{max} for the product is reached no earlier than four hours after administration.

9. A process for treating a bacterial infection in a host comprising: administering to a host the antibiotic product of Claim 1.

10. A process for treating a bacterial infection in a host comprising: administering to a host the antibiotic product of Claim 2.

11. A process for treating a bacterial infection in a host comprising: administering to a host the antibiotic product of Claim 3.

12. A process for treating a bacterial infection in a host comprising: administering to a host the antibiotic product of Claim 4.

13. A process for treating a bacterial infection in a host comprising: administering to a host the antibiotic product of Claim 5.

14. A process for treating a bacterial infection in a host comprising: administering to a host the antibiotic product of Claim 6.

15. A process for treating a bacterial infection in a host comprising: administering to a host the antibiotic product of Claim 7.

16. A process for treating a bacterial infection in a host comprising: administering to a host the antibiotic product of Claim 8.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/40809

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/00, 9/48,9/52, 9/54, 9/20, 9/22, 9/24, 9/14

US CL : 424/400, 451, 457, 458, 464, 468, 472, 489

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/400, 451, 457, 458, 464, 468, 472, 489

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,794,001 A (MEHTA et al) 27 December 1988 (27.12.1988), column 4, lines 21-39, examples, and figures.	1-16
Y	WO 98/22091 A1 (YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM) 28 May 1998 (28.05.1998), page 2.	1-16
Y	US 5,472,708 A (CHEN) 5 December 1995 (05.12.1995), column 5.	1-16
Y	US 5,011,692 A (FUJIOKA et al) 30 April 1991 (30.04.1991), column 4, line 10 and figures.	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
07 March 2003 (07.03.2003)	27 MAR 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Sharmila Gollamudi Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)

Continuation of B. FIELDS SEARCHED Item 3:
WEST, MEDLINE, DIALOG
search terms: pulsatile release, sustained release, Cmax, serum/plasma concentration